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Protocol

A Mobile Health Intervention for Patients With Depressive Symptoms: Protocol for an Economic Evaluation Alongside Two Randomized Trials in Brazil and Peru

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Abstract

Background: Mobile health interventions provide significant strategies for improving access to health services, offering a potential solution to reduce the mental health treatment gap. Economic evaluation of this intervention is needed to help inform local mental health policy and program development.

Objective: This paper presents the protocol for an economic evaluation conducted alongside 2 randomized controlled trials (RCTs) to evaluate the cost-effectiveness of a psychological intervention delivered through a technological platform (CONEMO) to treat depressive symptoms in people with diabetes, hypertension, or both.

Methods: The economic evaluation uses a within-trial analysis to evaluate the incremental costs and health outcomes of CONEMO plus enhanced usual care in comparison with enhanced usual care from public health care system and societal perspectives. Participants are patients of the public health care services for hypertension, diabetes, or both conditions in São Paulo, Brazil (n=880) and Lima, Peru (n=432). Clinical effectiveness will be measured by reduction in depressive symptoms and gains in health-related quality of life. We will conduct cost-effectiveness and cost-utility analyses, providing estimates of the cost per at least 50% reduction in 9-item Patient Health Questionnaire scores, and cost per quality-adjusted life year gained. The measurement of clinical effectiveness and resource use will take place over baseline, 3-month follow-up, and 6-month follow-up in the intervention and control groups. We will use a mixed costing methodology (ie, a combination of top–down and bottom–up approaches) considering 4 cost categories: intervention (CONEMO related) costs, health care costs, patient and family costs, and productivity costs. We will collect unit costs from the RCTs and national administrative databases. The multinational economic

evaluations will be fully split analyses with a multicountry costing approach. We will calculate incremental cost-effectiveness ratios and present 95% CIs from nonparametric bootstrapping (1000 replicates). We will perform deterministic and probabilistic sensitivity analyses. Finally, we will present cost-effectiveness acceptability curves to compare a range of possible cost-effectiveness thresholds.

Results: The economic evaluation project had its project charter in June 2018 and is expected to be completed in September 2021. The final results will be available in the second half of 2021.

Conclusions: We expect to assess whether CONEMO plus enhanced usual care is a cost-effective strategy to improve depressive symptoms in this population compared with enhanced usual care. This study will contribute to the evidence base for health managers and policy makers in allocating additional resources for mental health initiatives. It also will provide a basis for further research on how this emerging technology and enhanced usual care can improve mental health and well-being in low- and middle-income countries.

Trial Registration: ClinicalTrials.gov NCT12345678 (Brazil) and NCT03026426 (Peru); https://clinicaltrials.gov/ct2/show/NCT02846662 and https://clinicaltrials.gov/ct2/show/NCT03026426

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KEYWORDS

cost-effectiveness; depression; diabetes; hypertension; noncommunicable diseases; randomized trials; low- and middle-income countries; mHealth; task shifting; behavioral activation

Introduction

Globally, depression affects more than 264 million people each year, with a high prevalence in Brazil and Peru (5.8% and 4.8%, respectively). In Brazil, depressive disorders are ranked as the fourth leading cause of years lived with disability, and thirteenth for causing disability-adjusted life years [1]. In Peru, depressive disorders account for 37% of the years lived with disability attributed to mental health conditions and are responsible for almost 46,000 disability-adjusted life years [2].

Chronic diseases such as hypertension and diabetes can be exacerbated by depression, which is often undiagnosed and thus remains untreated [3,4]. This can lead reduced quality of life, increased physical health complications, and eventually a rise in treatment costs for both the individual and the health economy [4].

In low- and middle-income countries (LMICs) access to mental health care remains extremely limited and unequal, with those living in low-resource areas facing greater difficulties in accessing mental health care [5,6]. This is due to limited resource availability and a lack of trained health personnel. For instance, in Brazil there are only 4.48 specialists per 100,000 inhabitants. A similar scenario is observed in Peru, with 2.06 psychiatrists and 6 psychiatric nurses per 100,000 people [7]. Most Brazilians and Peruvians with clinically relevant levels of depressive symptoms currently do not receive any treatment. There is thus a clear need to address the mental health treatment gap within these settings.

Mobile health (mHealth) interventions offer potentially scalable and affordable solutions to reduce the treatment gap in mental health care (eg, depression). Studies on the effectiveness of mHealth intervention in this regard have shown promising results [8-11].

The Latin America Treatment and Innovation Network in Mental Health (LATIN-MH), 1 of 5 hubs funded by the National Institute of Mental Health (NIMH), conducted 2 randomized controlled trials (RCTs) evaluating the effectiveness of a low-intensity behavioral activation intervention for depression (CONEMO). These aimed to reduce symptoms of depression among individuals with hypertension, diabetes, or both conditions attending public health care facilities in São Paulo, Brazil, and Lima, Peru [12].

The acronym CONEMO is derived from the terms “Control” and “Emotional” (meaning: emotional control). The intervention is delivered via a smartphone app, and minimally supported by a nurse/nurse assistant (NA). The app consists of 18 brief mini-sessions, delivered automatically over a 6-week period, with 3 mini-sessions per week. Each session requires less than 10 minutes to complete [12]. The CONEMO intervention seeks to expand access to mental health care while using the available health services in Brazil and Peru [13].

Although efforts have been made to ensure the effectiveness, feasibility, and affordability of similar interventions, the success and impact are primarily determined by regional differences in cost structures and the burden of chronic diseases [14]. Cost data provide essential information for financial planning and enable decisions to be made regarding implementation feasibility. This cost analysis may provide a critical contribution to the planning and prioritization of interventions to address the large and growing burden of depression in LMICs.

Although there is an increase in economic evaluations of mHealth interventions, evaluations of these interventions in LMICs remain limited [15]. This paper describes a protocol for an economic evaluation to be conducted as part of 2 RCTs evaluating the cost-effectiveness of CONEMO, an mHealth intervention to treat symptoms of depression in people with diabetes or hypertension or both in Brazil and Peru.

Methods

Study Design

The economic evaluation will follow the Methodological Guidelines for Economic Evaluation Studies of Health Technologies [16] and will be reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [17]. The multinational economic evaluations will be fully split analyses (incorporating estimates of both resource use and clinical effectiveness from the same group of patients from individual countries) with a multicountry costing approach (applying unit cost estimates from individual countries to account for resource use in each of those countries) [18]. The within-trial analyses will be conducted using data from the randomized control trials NCT02846662 and NCT03026426, and secondary data on health service costs extracted from governmental public databases. This protocol outlines the methods for a cost-effectiveness analysis and cost-utility analysis alongside the RCTs conducted in Brazil and Peru, respectively.

The proposed economic evaluations will be conducted from both the public health care system perspective (including only health care system costs) and the societal perspective (including health care system costs plus patient and productivity costs).

Study Population

All participants in the RCT will be included in the economic evaluations. Participants include patients of the public health care system in Brazil or Peru. Inclusion criteria were adults (age ≥21 years), able to read the screen of a smartphone, receiving treatment for hypertension, diabetes, or both (self-report validated with clinical records), and experiencing symptoms of depression. Symptoms of depression were defined as obtaining a score of 10 or more on the 9-item Patient Health Questionnaire (PHQ-9) [19]. Participants were recruited from 20 primary care units in São Paulo, Brazil, and from 4 primary care centers and 3 outpatient clinics in Lima, Peru.

Setting and Location

The Brazilian health care system is made up of 2 subsectors: the National Health System (Sistema Único de Saúde [SUS]), which is universal and free for everyone, and private health insurance, which covers approximately 25% of the population. Peru has a decentralized health care system administered by 5 providers: the Ministry of Health (MINSA), which provides health services for 60% of the population; Social Security (EsSalud), which covers 30% of the population; and the Armed Forces (Fuerzas Armadas Españolas [FFAA]), Policía Nacional del Perú (PNP), and private sector, which together provide services to the remaining 10% of the population.

Both Brazilian and Peruvian health care systems have been implementing several reforms over the last 2 decades. As a result, health service networks in these countries are segmented into primary, secondary, and tertiary care levels [6,20]. Patients with diabetes and hypertension are typically seen within primary care in Brazil (primary care units) and within either primary (primary care centers) or secondary care units (hospital outpatient clinics) in Peru.

The trials have been conducted in primary care settings (20 public primary care centers of the SUS) in Sao Paulo, Brazil, and in 4 primary care centers in EsSalud and 3 outpatient clinics in MINSA in Lima, Peru [21].

Comparators

In the Brazilian and Peruvian health care systems, there is no screening policy for mental health in primary care units, where the focus is on physical health. Mental health care is available within specialized primary and secondary care services in both countries. The usual care in the primary care setting integrates practices of health promotion and clinical practice, which do not include the use of depression screening instruments.

The economic evaluations will compare CONEMO plus enhanced usual care with only enhanced usual care.

CONEMO Plus Enhanced Usual Care

The intervention group received CONEMO plus enhanced usual care. CONEMO is a low-intensity mHealth intervention aimed at reducing symptoms of depression. It is delivered via a smartphone app, and is minimally supported by a nurse/NA. The CONEMO app delivers 18 brief, automated mini-sessions over a 6-week period, with 3 mini-sessions per week. Each session is completed in less than 10 minutes.

The app content is based on behavioral activation, an evidence-based psychological approach to treat depression. Processed data on app usage were collected automatically and reviewed in real-time by nurses/NAs through a dashboard installed on tablets.

Nurses/NAs met with participants for an initial face-to-face meeting, where participants received a smartphone with the app preinstalled and completed a tutorial on its use. Nurses/NAs made 2 mandatory phone calls to all CONEMO participants at the beginning of the program to troubleshoot any difficulties and enhance motivation for the use of CONEMO. Additional calls were prompted through notifications sent to nurses/NAs when the CONEMO automated system detected nonadherence. Patients could request technical help through the help button on the app. Nurses/NAs received training and were supervised weekly by psychologists through face-to-face meetings or via telephone.

Enhanced Usual Care

The control group received the usual care plus the following procedures:

- Participants were screened using the PHQ-9 at baseline and at 3- and 6-month follow-ups.
- Those with a score of 10 or more on the PHQ-9 were advised to seek appropriate mental health care.
- Those presenting with suicide risk were referred to specialized mental health services, by either a health professional (in Sao Paulo and Lima) or the research team (in Lima). In Lima, relatives or health care professionals were also informed depending on risk severity.
- All participants received at least one call after screening at inclusion, and at 3- and 6-month follow-up from the research team to assess if they had sought specialized mental

health care. Those with higher risk or who did not seek care received additional phone calls.

Time Horizon and Discount Rate

Time horizon analyses will use the study follow-up period: 3 and 6 months after the inclusion of participants in the study in order to understand its permanence effect. We truncated time horizons to the length of follow-up in the RCTs because the long-term health outcomes remain unclear and are not expected to last beyond 6 months.

Following the recommendations of the Methodological Guidelines for Economic Evaluation Studies of Health Technologies [16], we will not apply the standard discount rate of 5% on costs and benefits, because of the short (<1 year) time horizons.

Choice of Health Outcomes and Measurement of Effectiveness

Table 1 summarizes the health outcome measures and time of collection for the outcomes that will be used in the economic evaluations.

Two health outcomes will be measured: reduction in symptoms of depression and health-related quality of life. First, the primary outcome of effectiveness for the cost-effectiveness analysis will be the proportion of patients with at least 50% reduction in PHQ-9 scores. This indicator has been used in many depression trials and is considered a robust way of symptom improvement [22].

Second, the EuroQol 5-dimensional questionnaire, 3-level version (EQ-5D-3L) will be used to measure health-related quality of life and provide utilities for estimation of quality-adjusted life years (QALYs). The EQ-5D-3L is a generic preference-based measure used in many clinical trials for a wide range of health conditions and treatments [23].

The measurement of clinical effectiveness will take place over 3 periods: baseline, 3-month follow-up, and 6-month follow-up. Both countries used the same measures (PHQ-9 and EQ-5D-3L).

Table 1. Summary of health outcomes measured.

Health outcomes	Measures	Timing of collection	Source of data
Depressive symptoms	PHQ-9[a]	Baseline, 3-month follow-up, and 6-month follow-up	Trials' patient-reported outcomes
Quality of life	EQ-5D-3L[b]	Baseline, 3-month follow-up, and 6-month follow-up	Trials' patient-reported outcomes

[a]PHQ-9: 9-item Patient Health Questionnaire.

[b]EQ-5D-3L: EuroQol 5-dimensional questionnaire, 3-level version.

Estimating Resources and Costs

The cost estimation will involve 3 stages: (1) identification of the costing items used to provide a particular service, (2) measurement of the resources used, (3) application of monetary value for each cost item, and calculation of the unit cost of a particular service [24].

The measurement of the resources will take place over 3 periods, baseline, 3-month follow-up, and 6-month follow-up, in the intervention and control groups. These are the same periods used to assess clinical effectiveness in the RCTs.

The measurement of resource use will be based on the group of patients from each country. The costing approach will apply unit cost estimates from Brazil and Peru to account for resource use in each of those countries.

Costs will be applied to the resources based on the unit costs or price weights most recently published in the respective official government databases (Department of Informatics of the National Health System, Departamento de Informática do Sistema Único de Saúde [DATASUS] in Brazil; and the Integral Health Insurance/Seguro Integral de Salud [SIS] in Peru). Other resource use not recorded in DATASUS or SIS will be based on LATIN-MH databases. These costs will be obtained in Brazilian reals (R$) and Peruvian sols (S$), as per rates in 2017. All costs will be adjusted for inflation using the Brazilian and Peruvian consumer price indexes for the current reference year (2021) and will be converted into international dollars (INT$) using the 2021 purchasing power parity (PPP) conversion factors for Brazil and Peru.

We will use a mixed costing methodology (ie, a combination of top–down and bottom–up approaches) considering 4 cost categories: intervention (CONEMO related) costs, health care costs, patient and family costs, and productivity costs. Table 2 presents an overview of resource use and cost measures that will be used in the economic evaluations. These include costs hypothesized to differ between CONEMO plus enhanced usual care (the intervention group) and enhanced usual care (the control group).

Table 2. Summary of cost categories measured.

Cost category and unit		Unit cost	Source of data
Intervention (CONEMO[a]) costs			
Staff involved in supervision	Hour of supervision	Cost/hour	LATIN-MH[a] databases
Staff involved in training	Hour of a research assistant	Cost/hour	LATIN-MH databases
Transport	Number of trips	Cost/trip	LATIN-MH databases
Dashboard and app maintenance	Maintenance charge	Cost/month	LATIN-MH databases
Internet package	Monthly package	Cost/month	LATIN-MH databases
Office supplies		Cost/month	LATIN-MH databases
Infrastructure		Cost/month	LATIN-MH databases
Health care costs			
Psychiatrist visits	Number of visits	Cost/visit	CEI[b] and ISSM[c]
Family physician visits	Number of visits	Cost/visit	CEI and ISSM
Psychologist visits	Number of visits	Cost/visit	CEI and ISSM
Emergency room visits	Number of visits	Cost/visit	CEI, ISSM, and SAEs[d]
Hospital admissions	Number of hospital admissions	Cost/hospital admission	CEI, ISSM, and SAEs
Medicines	Number of doses	Cost/dose	CEI and ISSM
Patient and family costs			
Transport	Number of trips	Cost/trip	Average cost for public transport
Internet	Monthly package	Cost/month	Average market price
Productivity costs			
Days of work lost	Number of days	Cost/hour	Average hourly wage

[a]CONEMO: control emotional (emotional control intervention).

[b]LATIN-MH: Latin America Treatment and Innovation Network in Mental Health.

[c]CEI: Cost-Effectiveness Instrument.

[d]Mental Health Instrument.

[e]SAE: Serious Adverse Events Report.

Intervention Costs

Intervention costs include the value of the staff time and transport involved in either supervision or training of the primary care workers that will use CONEMO.

We will assume that the intervention (CONEMO) is operational, and so start-up costs, such as design and development of CONEMO, will be excluded. Therefore, we will include only costs for maintenance of the dashboard and app, internet package costs, and expenditures related to office supplies and infrastructure.

All of the research-related costs associated with trial administration, data collection, and outcome assessment of RCTs will be excluded.

Health Care Costs

Health care costs will include direct medical costs: outpatient visits, emergency room and hospital admissions, and medicines prescribed during the study period.

Patient and Family Costs

Patient and family costs will include direct nonmedical costs, such as transport for seeking health care and internet expenditures. In São Paulo, we will assume that for each hospital admission, there will be 2 public transport trips. For those aged over 60, we will add a companion cost (according to Article 16 of the Brazilian Elderly Statute) [25]. In case of attendance at the primary care centers, no transportation cost will be calculated, as we are assuming participants will be attending a local service. In Lima, we will consider the use of 2 public transport trips for all participants. For participants aged over 60, considering the lack of specific regulations, we agreed on including an additional 50% cost for caregiver transportation.

We assumed that the patients already own a smartphone and included only the costs of internet access.

Productivity Costs

Productivity costs will include indirect costs related to lost days of work due to morbidity and will be estimated according to the human capital approach [26]. Productivity costs associated with depressive symptoms will be calculated by multiplying

the number of hours absent with an average hourly wage in Brazil and Peru.

Policy Statement, Data Analysis, and Security Responsibilities

The RCTs were approved by the Data and Safety Monitoring Board (DSMB) of the NIMH, USA, and local ethics committees in São Paulo and Lima.

Primary data (phase 1) were collected on ethical standards and underwent internal and external audit by the DSMB. Secondary data (phase 2) will follow the same guidelines for quality purposes.

Informed consent was obtained from participants by the research team at screening and baseline. Consent for this study was obtained as part of the RCT procedures.

Study coordinators (DdS and PS) will carry out the collection and analysis of secondary data from each country with the support of the LATIN-MH Data Center team and a specialized consultant under the supervision of the principal investigators (PM and RA). Data sets will be anonymized by removing personal identifiers (eg, name, phone number) to protect the confidentiality of study participants.

Analytic Methods

Mean values of the estimated health outcomes and costs, as well as mean differences between the comparator groups (CONEMO plus enhanced usual care versus enhanced usual care) will be reported. Incremental cost-effectiveness ratios (ICERs) will be calculated as the arithmetic mean difference in cost between CONEMO plus enhanced usual care and enhanced usual care, divided by the arithmetic mean difference in effect. For the cost-effectiveness analysis, the corresponding ICER will be expressed as the incremental costs per at least 50% reduction of PHQ-9 scores. In the cost-utility analysis, the ICER will be expressed as the incremental costs per QALY gained. ICERs will be generated by nonparametric bootstrapping methods using random resamples for every 1000 pairs of outcomes and costs for the intervention and comparator groups to derive 95% CIs [27]. The distribution of mean incremental costs and outcomes shown on cost-effectiveness will be conducted to test the robustness of results.

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses will be performed to determine the level of confidence around the resulting ICERs. Several deterministic (1 way) sensitivity analyses will be carried out by varying the key parameters (such as quantity of resource use, unit cost of resource use, QALYs) in the within-trial analyses. Results from deterministic sensitivity analyses will be presented in a tornado diagram to compare the relative importance of the parameters with the ICER. The results from the probabilistic sensitivity analysis will also be presented using cost-effectiveness acceptability curves [28]. This curve indicates the probability that the CONEMO plus enhanced usual care is cost-effective compared with enhanced usual care, considering the thresholds range of $PPP3210-$PPP10,122 per QALY gained for Brazil, and of $PPP1969-$PPP7747 per QALY gained for Peru [29].

Statistical Software Use for Health Economic Analysis

Stata (StataCorp) version 15.0 or higher will be used for all health economics analyses.

Results

Phase 1 of the project ran from September 2016 to April 2018 to assess the applicability of CONEMO. Phase 2 began in June 2018 and is expected to be completed in September 2021. The economic evaluation of CONEMO will be conducted during this phase. Results will be used to report the costs of CONEMO to help plan the implementation of the intervention. The evaluation will also calculate the cost-effectiveness of CONEMO to improve symptoms of depression.

Discussion

Overview

Assessing the economic viability of the CONEMO intervention based on its cost-effectiveness will enable us to ascertain the feasibility of its implementation in primary and secondary care. If shown to be financially viable, the intervention could help bridge the treatment gap and increase access to mental health care. If the ICER is favorable, there would be a strong case for policymakers to support the scale-up of this intervention.

Implementing the CONEMO intervention would enable the screening, identification, and treatment of depression in patients with chronic diseases. The expected result is a reduction in symptoms and likely an increase in self-care, adherence to treatment, and quality of life. These outcomes could also result in fewer complications and required resources, as well as reduced health care costs. Using nursing staff to support patients rather than specialized mental health professionals and specialized services could also be an efficient use of human resources, thereby saving costs in the longer term.

Economic evaluations are particularly important because they can be used to guide decision makers or funders in determining if the mHealth interventions improve health outcomes when compared to other existing interventions [15]. They are also important for analyzing whether the cost to adopt and maintain the intervention in a health system is justified. One of the barriers of mHealth implementation and scale-up is the financial feasibility, yet few studies include or detail operational costs of mobile communication, such as fees charged to end users (patients).

Generalizability and Future Research

If found to be clinically effective and cost-effective, CONEMO could be used in other populations with similar treatment gaps [13]. Replication has been made possible by the standardized materials used. The generalizability of results is likely high due to the diverse in-country heterogeneous sample and its implementation in 2 countries.

- Implications for health provision and use: We would seek to collaborate with other services to develop further evidence for implementation.

- Implications for health policies: Despite some limitations, this protocol will be used to measure the costs of mental health services in 2 studies, generating data to support local mental health policies, boost research in the country, and support new studies.

Study Limitations

Health economic evaluation studies on mHealth interventions have not been conducted in Brazil and Peru; while this is an innovative research study, some limitations remain. These are as follows:

- Cost-effectiveness analysis may be hampered by the scarcity of economic and epidemiological data available and the composition of the variables for each cost when found.
- Peruvian analysis will follow Brazilian guidelines due to the lack of guidelines for health economic evaluation in Peru.
- Some cost items will be based on other similar items, which do not express the same precision level of a specialized service sample collected on official cost indicator databases.
- Difficulty in including all indirect costs incurred from the societal perspective due to insufficient information related to the treatments under analysis.

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Authors' Contributions

PM and RA are the principal investigators of the study and participated on the first draft and final approval of the manuscript, as well as obtained funding. DdS and PdS are responsible for the study concept and design. All authors were participated in the drafting of this manuscript and in its critical revision for important intellectual content.

Conflicts of Interest

None declared.

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Abbreviations

CONEMO: control emotional (emotional control intervention)

DATASUS: Departamento de Informática do Sistema Único de Saúde (Department of Informatics of the National Health System)
EQ-5D-3L: EuroQol 5-dimensional questionnaire, 3-level version
FFAA: Fuerzas Armadas
ICER: incremental cost-effectiveness ratio
LATIN-MH: Latin America Treatment and Innovation Network in Mental Health
LMIC: low- and middle-income countries
mHealth: mobile health
NA: nurse assistant
PHQ-9: 9-item Patient Health Questionnaire
PPP: purchasing power parity
QALY: quality-adjusted life year
RCT: randomized controlled trial
SIS: Seguro Integral de Salud (Integral Health Insurance)

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Protocol

Text Messaging Versus Email Messaging to Support Patients With Major Depressive Disorder: Protocol for a Randomized Hybrid Type II Effectiveness-Implementation Trial

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Abstract

Background: Major depressive disorder (MDD) accounts for 40.5% of disability-adjusted life years caused by mental and substance use disorders. Barriers such as stigma and financial and physical access to care have been reported, highlighting the need for innovative, accessible, and cost-effective psychological interventions. The effectiveness of supportive SMS text messaging in alleviating depression symptoms has been proven in clinical trials, but this approach can only help those with mobile phones.

Objective: This paper presents the protocol for a study that will aim to evaluate the feasibility, comparative effectiveness, and user satisfaction of daily supportive email messaging as an effective strategy compared to daily supportive text messaging as part of the treatment of patients with MDD.

Methods: This trial will be carried out using a hybrid type II implementation-effectiveness design. This design evaluates the effectiveness of an implementation strategy or intervention, while also evaluating the implementation context associated with the intervention. Patients with MDD receiving usual care will be randomized to receive either daily supportive email messaging or daily supportive text messaging of the same content for 6 months. The Patient Health Questionnaire-9, the Generalized Anxiety Disorder-7, and the 5-item World Health Organization Well-Being Index will be used to evaluate the effectiveness of both strategies. The implementation evaluation will be guided by the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework, as well as the Consolidated Framework for Implementation Research. All outcome measures will be analyzed using descriptive and inferential statistics. Qualitative data will be analyzed using thematic analysis.

Results: Data collection for this trial began in April 2021. We expect the study results to be available within 18 months of study commencement. The results will shed light on the feasibility, acceptability, and effectiveness of using automated emails as a strategy for delivering supportive messages to patients with MDD in comparison to text messaging.

Conclusions: The outcome of this trial will have translational impact on routine patient care and access to mental health, as well as potentially support mental health policy decision-making for health care resource allocation.

Trial Registration: ClinicalTrials.gov NCT04638231; https://clinicaltrials.gov/ct2/show/NCT04638231

International Registered Report Identifier (IRRID): DERR1-10.2196/29495

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KEYWORDS

email messaging; text messaging; supportive; major depressive disorder; randomized trial; mental health; digital health; mobile health; mHealth; patient care; health policy; decision-making; health care resources

Introduction

Background

Depression is a debilitating condition characterized by changes in mood, self-attitude, cognitive functioning, sleep, appetite, and energy levels [1,2]. Decreases in the quality of life associated with depression leads to impairment in occupational and social functioning [2,3]. In 2010, it was estimated that mental and substance use disorders were the leading cause of years lived with disability worldwide, with depressive disorders accounting for 40.5% of disability-adjusted life years caused by mental and substance use disorders [4]. Depression is thus a major contributor to the overall global burden of disease [4-6], and it is projected by the World Health Organization that major depressive disorder (MDD) will be the leading cause of disability worldwide by 2030 [7].

In 2012, over 3.2 million Canadians over 15 years of age (11.3%) reported symptoms of major depression, which is associated with higher health and service utilization than most other patients [8]. Psychosocial interventions and pharmacotherapy are among preferred first-line treatments for severe mental health problems including major depression [9]. Psychotherapies, such as cognitive behavior therapy, interpersonal psychotherapy, problem-solving, and behavioral activation are common and effective forms of treatment for depression [9]. However, access to these psychotherapies is limited by human resource capacity constraints, which leaves the majority of people with depressive disorders untreated [10,11]. Access is further limited by geographic location as psychosocial services are also more frequently available in cities and towns [12], with far less access for rural inhabitants [13]. Even in cities and towns, these services are mostly only available during the working days and day-time business hours [8,14], with caregivers often dealing with twice the recommended number of clients, further restricting appointment availability [14]. Long wait-times to access counseling services and the stigma associated with seeking mental health counseling also compound the problem. In the 2012 Canadian Community Health Survey on Mental Health, barriers such as lack of a readily available care system, stigma, and affordability of health care services were reported by 2.3 million Canadians, who expressed they had unmet or partially met mental health care needs [15,16]. It is clear that the traditional ways of providing mental health care alone will not be able to meet the demands for services given that the prevalence of depression is so high and not likely to decrease any time soon [17]. Consequently, there is a need to develop innovative psychological interventions that are not human resource intensive, and are easily accessible, cost-effective, independent of geographic location, scalable, and can be offered to thousands of people simultaneously.

Digital technologies for the provision of health care interventions have advanced significantly in the last decade, and further development of this field looks very promising [18]. Current evidence supports the efficacy and cost-effectiveness of these new technologies, such as tele–mental health, as they may enhance access to mental health care and contribute to closing the treatment gap that has existed over the years [19,20]. Useful communication methods for the delivery of mental health services have included smartphone apps, text messages, and email [20,21]. There is therefore a need for the health profession to embrace these new trends of digital technological care, particularly in the domain of mental health [22].

Intervention and Implementation Strategies

eHealth approaches have been rapidly expanding in recent decades, with evidence indicating that the provision of internet-based mental health services is clinically effective [23] and cost-effective even though many health professionals have, until quite recently, been slow to engage in this clinical domain [24,25]. Supportive text messages have also become increasingly accepted as an appropriate and acceptable means of delivering psychological care to patients with mental health issues [26]. It is estimated that 99% of received text messages are opened, and 90% of all text messages are read within 3 minutes of reception [27], presenting an accessible opportunity to close the psychological treatment gap for patients with depression [28]. In 3 randomized controlled trials conducted in Ireland [29] and Canada [30], patients with MDD who received twice-daily supportive text messages had significantly greater reductions in their depression symptom scores than patients who received treatment as usual. In the first of the 2 studies conducted in Ireland, after 3 months, the mean difference in Becks Depression Inventory-II (BDI-II) scores between the intervention and control groups was –7.9 (95% CI –13.06 to –2.76, Cohen *d*=0.85) in favor of the intervention group [29]. Similar results were reported in another Irish study with a larger sample size and, after 3 months of exposure, a Canadian study reported a significant difference in mean BDI-II scores for the intervention versus control groups (mean 20.8, SD 11.7 vs mean 24.9, SD 11.5, respectively; $F_{1,60}$=4.83, *P*=.03, η_p^2=0.07) with an effect size (Cohen *d*) of 0.67 [30]. A recent literature review of studies conducted on the effectiveness of text messaging as an adjunct therapy for mothers with postpartum depression living in low-income countries also reported a positive outcome [31], where the mothers showed a preference for receiving psychological care via text messaging [32]. Several studies reported high user satisfaction with a supportive text message intervention [28,33], and in one of these studies, 83% of subscribers to the Text4Mood program reported that daily messages contributed to improving their overall mental well-being [28].

Though patronage of supportive text messaging programs is deemed great in most cases due to the high numbers of subscribers, anecdotally, some people were unable to subscribe to supportive text messaging programs such as Text4Hope [33]

and Text4Mood [28] because they did not have active mobile phone numbers, including several individuals for whom these programs were recommended by Addiction and Mental Health clinics in Edmonton resulting in inquiries as to whether the messages could be sent to them via email. In the participants' satisfaction survey for the Text4Hope program, the majority of respondents (64%) were in favor of email messaging as part of their health care support during crisis periods despite having access to mobile phones.

With the rise of eHealth apps, email has been established as a secure avenue of communication, increasingly used for interactions between physicians and their patients [34]. The uniqueness of email messaging can be linked to its special characteristics, including flexibility of message length, asynchronous communication, and rapid message delivery [18]. There is a lack of data on whether email messaging is as effective as text messaging to clinically support patients with MDD.

Study Aims and Objectives

The *Supportive Text vs Email Messaging* (STEM) trial aims to evaluate comparatively the implementation and impact of two implementation strategies (text messaging and email messaging) for delivering supportive messages to patients with MDD.

The specific objectives are outlined below:

1. Implementation evaluation:
   - To compare the impact of both strategies for delivering the daily supportive messages on implementation outcomes (adoption, fidelity, reach, cost, sustainability);
   - To evaluate contextual factors that could inhibit or facilitate the implementation of each strategy.
2. Clinical effectiveness evaluation:
   - To compare the mean difference in Patient Health Questionnaire-9 (PHQ-9) [35] scores from baseline and at 6, 12, and 24 weeks for patients with MDD receiving standard care plus daily supportive email messages to those receiving standard care plus daily supportive text messages;
   - To compare the quality of life using the 5-item World Health Organization Well-Being Index (WHO-5) [36] at baseline and at 6, 12, and 24 weeks for patients with MDD receiving standard care plus daily supportive email messages to those receiving standard care plus daily supportive text messages;
   - To compare anxiety levels using the Generalized Anxiety Disorder-7 (GAD-7) scale [37], at baseline and at 6, 12, and 24 weeks, as well as the dropout and satisfaction rates between patients in the two treatment arms.

Methods

Study Design

The STEM study design is a mixed methods, hybrid type II implementation-effectiveness trial. This design evaluates the effectiveness of an implementation strategy or intervention, while also evaluating the implementation context associated with the intervention [38,39]. This study is a randomized noninferiority trial testing the outcomes for email messaging (as a strategy for delivering daily evidence-based supportive messages to patients with MDD in addition to usual care), in comparison to outcomes for text messaging, which has been deemed effective by previous studies (with noted implementation limitations [28,33]). The relevant guidelines and checklist were obtained from the Enhancing the Quality and Transparency of Health Research (EQUATOR) network website and used in the design of this trial [40]. These include the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 1) and CONSORT (Consolidated Standards of Reporting Trials) guidelines (Multimedia Appendix 2) [41,42].

Study Settings

Patients will be recruited from the Alberta Health Services Access 24/7 clinic located in Edmonton, Canada. This city center Access 24/7 clinic is a zone-wide centralized intake clinic for addiction and mental health. Patients with mental health concerns can self-present or are referred by a primary care provider to the clinic for assessments and referral to other community mental health clinics for follow-up or to other community support services as necessary.

Participant Recruitment

Patients who have been assessed by a psychiatrist at the Urgent Psychiatric Clinic of the Access 24/7 clinic in Edmonton and diagnosed with an MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria using a structured clinical interview will be offered an information leaflet about the study and invited to participate.

Inclusion Criteria

The inclusion criteria are as follows:

1. Persons aged 18 to 65 years who have the capacity to provide informed consent;
2. Patients who have been assessed using structured clinical interviews for DSM-5 and diagnosed with an MDD;
3. Patients who have a mobile phone with an active line and a functional email address and can access both email messages and text messages;
4. Patients who willingly agree to be enrolled in the trial and sign the consent form.

Exclusion Criteria

Patients will be ineligible if they are patients with active psychotic disorders or residing outside of regular mobile phone and internet connection areas. They will also be ineligible if they previously or currently subscribed to Text4Hope, Text4Mood, Text4Support, or another supportive text messaging program.

Sample Size

Based on the effect sizes (Cohen *d* of 0.85 and 0.67) achieved in 2 previous randomized trials (n<80 for each trial), which compared daily supportive text messages plus treatment as usual with treatment as usual alone for the management of patients with MDD, a sample size of 80 is estimated to have sufficient

power for the current protocol. Allowing for a projected maximal 20% overall dropout rate, we propose to recruit 100 patients with MDD into the trial, with 50 patients randomly allocated into each study arm.

Randomization and Blinding

We will use computer-generated block randomization to ensure balance (1:1) between the two treatment groups. Randomization codes will be provided via text message directly to the blinded researcher's password-protected phone line with a secure online backup. This will occur for enrollment as each participant signs the consent form. All study participants will complete baseline assessments before randomization, and follow-up assessments will occur through online surveys with the survey links delivered via text messaging or email messaging depending on which study arm participants belong to. Participants will be asked to use either the email address or phone number with which they receive messages as their study ID on the follow-up online surveys.

Intervention and Implementation Strategies

A research coordinator will assist participants who have provided written informed consent to enroll in either the email messaging or text messaging program by inputting their email address or phone number into the online email messaging or text messaging platforms that will be used to deliver the daily messages. Starting a day after enrollment, participants will receive either daily supportive text messages or daily supportive email messages. Both the email and text messages have the same content and have been crafted by mental health therapists, clinical psychologists, psychiatrists, and mental health service users based on cognitive behavior therapy principles. Each message will be scheduled to be delivered to the participants' mobile phone or email address at 10 AM MT, and each participant will receive the messages for 6 months.

Conceptual Framework

This hybrid trial will evaluate and compare both the effectiveness of each STEM strategy (supportive text messaging and email messaging) as well as context, process, and outcomes of the implementation. The trial will integrate two implementation science frameworks to guide the evaluation:

1. The RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [43], which comprises five domains, will be used to assess external validity and feasibility of scale-up.
2. The Consolidated Framework for Implementation Research (CFIR) [43,44] will be used to systematically assess contextual factors (barriers and facilitators) that influence the adoption and implementation of the strategies. The CFIR guides the evaluation of contextual influences on intervention implementation and consists of five domains: intervention characteristics, outer setting, inner setting, characteristics of individuals, and process of implementation.

Figure 1 is an illustration of the evaluation framework of the STEM trial, while Table 1 is an overview of the outcome measures.

Figure 1. Conceptual framework of the *Supportive Text vs Email Messaging* (STEM) trial informed by the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) and Consolidated Framework for Implementation Research frameworks. PHQ-9: Patient Health Questionnaire-9, WHO-5: 5-item World Health Organization Well-Being Index, GAD-7: Generalized Anxiety Disorder-7.

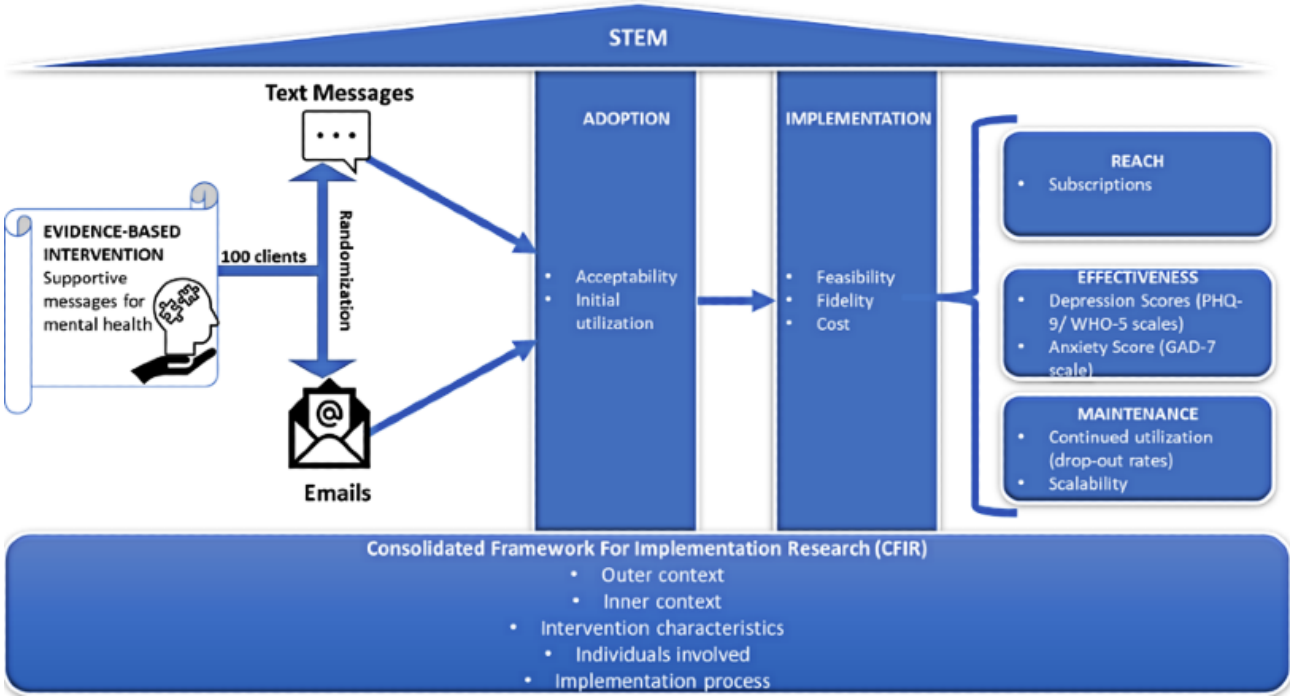

Table 1. Overview of the *Supportive Text vs Email Messaging* (STEM) outcome measures.

RE-AIM[a] domain and outcomes	Measures	Data source	Timeline (months)					
			1-3	4-6	7-9	10-12	13-15	16-18
Reach								
Dose delivered	The frequency of emails and text messages sent to the subscribers (including delivery failures)	STEM metadata	✓	✓	✓	✓	✓	✓
Dose received	The average number of times participants read the emails or text messages	Survey questionnaire			✓	✓	✓	✓
Effectiveness								
Depression symptom score	Patient Health Questionnaire-9 (PHQ-9)	Clinical questionnaire			✓	✓	✓	✓
Patients' quality of life	5-item World Health Organization Well-Being Index (WHO-5)	Clinical questionnaire			✓	✓	✓	✓
Anxiety symptom scores	Generalized Anxiety Disorder-7 (GAD-7)	Clinical questionnaire			✓	✓	✓	✓
Adoption								
Acceptability/uptake	The number of subscriptions to the text and email services	STEM metadata						✓
Acceptability/uptake	Barriers and facilitators	Qualitative focus group discussions guided by the CFIR[b]						✓
Implementation								
Feasibility	Implementation drivers (barriers and facilitators)	Qualitative focus group discussions guided by the CFIR						✓
Fidelity	The proportion of participants who read the messages at least once a day	Survey questionnaire			✓	✓	✓	✓
Cost	Comparative cost of developing and maintaining both strategies	STEM metadata	✓	✓	✓	✓	✓	✓
Maintenance								
Sustainability	Dropout rates; barriers and facilitators	Subscription data; qualitative focus group discussions guided by the CFIR						✓

[a]RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

[b]CFIR: Consolidated Framework for Implementation Research.

Effectiveness Evaluation

Hypothesis

As the same messages will be delivered through the supportive text message program and the email program, we hypothesize that daily email messaging will not be inferior to daily supportive text messaging in reducing depression symptoms and improving quality of life for patients with MDD. We further hypothesize that participant dropout rates and satisfaction rates will be comparable in the two arms of the study.

Data Collection

Participants who provide informed written consent and agree to participate in the study will be asked to complete a baseline assessment questionnaire that captures both demographic and clinical information. At 6, 12, and 24 weeks, an online survey link will be sent to participants via email or text messages along with an invitation for them to complete the assessments. Participants will enter the email address or phone number through which they receive the messages as their study identifier at the start of the survey so that their data at the 4 time points can be matched. Participants who have not completed their follow-up assessments within 3 days of the due date will be contacted by a research coordinator and reminded to do so, or

if they require assistance to complete the assessment, such assistance will be offered, including the option to complete the assessment over the telephone. In instances where such assistance is required, a blinded research assistant will be asked to read out the survey questions to the participant and record their responses.

Outcome Measures

The primary effectiveness outcome measures for the study will be the differences between mean scores on the following scales measured at baseline, 6, 12, and 24 weeks for the two study arms: the PHQ-9, WHO-5, and GAD-7.

The PHQ-9 scale will be used to provide depression symptom scores [35]. The PHQ-9 is a 9-item validated instrument (associated with a Cronbach alpha of .89) that is used to diagnose and measure the severity of depression in general medical and mental health settings. Each of the 9 questionnaire items is scored between 0 (not at all) to 3 (nearly every day). Higher scores on the scale indicate higher levels of depression. The PHQ-9 demonstrated good convergent validity with related constructs with an adequate internal consistency [45].

The WHO-5 will be used to measure patients' quality of life [46]. The WHO-5 is a short 5-item questionnaire that measures the subjective well-being of the respondents. The scale has adequate validity as an outcome measure in clinical trials and as a generic scale for assessing well-being over time or between groups [47].

Secondary outcomes include changed mean scores on the GAD-7 scale [37] at baseline, 6, 12, and 24 weeks for the two study arms, as well as participant dropout rates and satisfaction rates at 12 and 24 weeks in the two arms. The GAD-7 is a validated 7-item questionnaire (associated with a Cronbach alpha of .92) that is used to assess the self-reported levels of anxiety in respondents in the 2 weeks prior to assessment. Each item on the scale is scored between 0 (not at all) to 4 (nearly every day). Higher scores on the scale indicate higher levels of anxiety.

Data Analyses

We will summarize the baseline demographic and clinical characteristics of participants in raw values and percentages and compare them between the two treatment arms using chi-square or Fisher exact tests and appropriate *t* tests. The primary and secondary outcome measures will be analyzed using descriptive and inferential statistical analysis. For the primary outcome measures, we will use analysis of covariance (ANCOVA) to assess the change in scores between the two treatment arms, with baseline PHQ-9 and WHO-5 scores as covariates; the treatment arm as the independent variable; and PHQ-9 and WHO-5 scores at 6, 12, and 24 months as respective dependent variables for each time point. Secondary quantitative outcome measures will be compared using chi-square or Fisher exact tests and appropriate *t* tests.

Implementation Evaluation

Implementation evaluation will seek to explore and compare the context, process, and outcomes of implementing the two strategies, guided by the CFIR and the RE-AIM frameworks. A mixed method approach will be applied in evaluating the implementation of the STEM trial.

Data Collection

Quantitative data will be collected on the implementation outcomes: acceptability, fidelity (adherence to reading messages), and sustainability (continued utilization). Data will be collected using user satisfaction survey questionnaires at 6, 12, and 24 weeks for the two study arms.

Qualitative data will be collected via focus group (see details below) discussions involving the patients. The discussion topic guide will be informed by the CFIR domains and will also elicit participants' views on barriers and facilitators to the implementation of both strategies.

We will invite a random sample of 10 participants via text message and email to take part in a virtual focus group workshop using end-to-end encrypted teleconferencing (with appropriate consent for confidentiality) to discuss the impacts of the interventions. In order to explore the reasons why participants remain or drop out of the study, we will hold a focus group for a cross-section of participants who remained in the study and those who dropped out to discuss the impacts of the supportive email and text message interventions. Thus, an invitation will go to both those who remain in the study and those who dropped out, and participation in the focus group workshop will be voluntary. We will offer a CAD $50 (US $39) gift card as honorarium to cover the cost for participants attending the focus group.

Data Analysis

Quantitative data will be analyzed as described under "Effectiveness Evaluation" section. Qualitative data obtained through audio recordings from the patient focus group discussions will be transcribed, then analyzed using thematic analysis aided by NVIVO software (QSR International). Data analysis will be both deductive and inductive. Deductive analysis will be guided by the CFIR and RE-AIM. Two researchers will independently conduct the initial coding after familiarization with the transcripts; thereafter, the subsequent and final coding criteria will be agreed upon by both researchers following an iterative review of emerging themes as informed by the research questions. The final sets of themes and subthemes relevant to the overall research goals will be reported and supported with verbatim quotes.

Addressing Missing Data

Though preventing missing data is difficult in clinical research, measures will be put in place by the researchers to minimize the occurrence of missing data. This includes having a well-defined data collection strategy that is understood by all study personnel, as well as having a simple set of questionnaires to collect only relevant data needed, minimizing the number of follow-ups with participants, and creating substantial gaps in the number of follow-ups. The investigators will identify and actively engage the participants who would be at the greatest risk of being lost during follow-up. Further, the data collection would be monitored and reported in as close to real time as possible during the study. Notwithstanding the above, the mean substitution strategy would be employed by the research team

to handle missing data [48]. Here, the mean value of a variable is used in the place of the missing data value for that same variable. This allows the researchers to utilize the collected data in an incomplete data set. Questionnaires with more than 20% missing responses will be excluded.

Gender Analysis

Gender analyses will guide the entire study. Beyond gender disaggregation and adjustments to accommodate potential differences in subscription, the development and adaptation of the supportive messages will receive input from gender specialists. Further, the implementation science framework CFIR is designed to accommodate and understand gender among the characteristics of individuals involved in intervention implementation.

Ethics and Dissemination

All study participants will be provided with an information leaflet and offered the opportunity to ask questions about the study before being asked to provide written informed consent to participate in the study. Data collection will occur online through patient self-completed rating scales. The study has received institutional review board approval from the University of Alberta Human Ethics Review Board (Pro00105429), and the trial has been registered at ClinicalTrials.gov (NCT04638231). Results will be disseminated as publications, conference presentations, and stakeholder policy dialogues.

Results

Data collection for this trial began in April 2021. We expect the study results to be available within 18 months of study commencement. The findings of the trial are expected to shed light on the feasibility, acceptability, and effectiveness of using automated emails as a strategy for delivering supportive messages to patients with MDD in comparison to text messaging.

Discussion

Implications of the Study

Supportive messaging may be effective for providing patient support for various mood disorders. It is accepted that this intervention can reduce demand for physical mental health services, particularly the need to seek acute mental health care at emergency departments [28,30,33].

As previous studies have delivered these messages using text messaging services on mobile devices, this study seeks to examine the effectiveness of email-based delivery of equivalent messages. The STEM trial will provide comparative evidence on both delivery strategies as well as useful information to inform us on how to better implement them at scale. Findings from this study will be useful for mental health professionals managing MDD, and will contribute to knowledge on eHealth approaches generally. During the current COVID-19 pandemic, this is particularly important as health care agencies seek alternatives to physical contact where possible [49,50].

The external validity of this trial is limited by the single catchment site context. Despite this, findings from this trial will inform the implementation of a planned full-scale multicenter clinical trial using Resilience N Hope [51] to determine the effectiveness of this strategy across various contexts. The limitations are mitigated by the mixed methods approach to the design. It is hoped that the triangulation of findings from both quantitative and qualitative methods will provide useful insights. In addition, the proposed application of implementation science frameworks will provide practical information to inform implementation at scale. Unavoidably, the study sample might experience a considerable selection bias, based upon the necessity of having a functioning mobile phone and an email address in order to be able to participate in the study. Thus, this bias may limit the generalizability of our findings as patients who lack these prerequisites will not necessarily be represented in here.

Conclusion

The STEM trial is expected to inform effective and contextually feasible strategies for delivering supportive messages to patients with MDD. The outcome of this trial will have translational impact on routine patient care and access to mental health as well as potentially support mental health policy decision-making for health care resource allocation.

Acknowledgments

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Authors' Contributions

VIOA conceived and designed the study. MKA, RS, and EE jointly drafted the initial manuscript with VIOA. AS, NN, RC, FO, CC, MA, PC, and AJG critically reviewed the manuscript and contributed to the final draft. All authors reviewed and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The SPIRIT checklist.

[DOCX File , 17 KB - resprot_v10i10e29495_app1.docx]

Multimedia Appendix 2
CONSORT 2010 checklist.
[DOCX File , 40 KB - resprot_v10i10e29495_app2.docx]

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Abbreviations

ANCOVA: analysis of covariance
BDI-II: Becks Depression Inventory-II
CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials
DSM-5: Diagnostic and Statistical Manual of Mental Disorders
EQUATOR: Enhancing the Quality and Transparency of Health Research
GAD-7: Generalized Anxiety Disorder-7
MDD: major depressive disorder
PHQ-9: Patient Health Questionnaire-9
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STEM: Supportive Text vs Email Messaging
WHO-5: 5-item World Health Organization Well-Being Index

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Protocol

Remote Mobile Outpatient Monitoring in Transplant (Reboot) 2.0: Protocol for a Randomized Controlled Trial

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Abstract

Background: The number of solid organ transplants in Canada has increased 33% over the past decade. Hospital readmissions are common within the first year after transplant and are linked to increased morbidity and mortality. Nearly half of these admissions to the hospital appear to be preventable. Mobile health (mHealth) technologies hold promise to reduce admission to the hospital and improve patient outcomes, as they allow real-time monitoring and timely clinical intervention.

Objective: This study aims to determine whether an innovative mHealth intervention can reduce hospital readmission and unscheduled visits to the emergency department or transplant clinic. Our second objective is to assess the use of clinical and continuous ambulatory physiologic data to develop machine learning algorithms to predict the risk of infection, organ rejection, and early mortality in adult heart, kidney, and liver transplant recipients.

Methods: Remote Mobile Outpatient Monitoring in Transplant (Reboot) 2.0 is a two-phased single-center study to be conducted at the University Health Network in Toronto, Canada. Phase one will consist of a 1-year concealed randomized controlled trial of 400 adult heart, kidney, and liver transplant recipients. Participants will be randomized to receive either personalized communication using an mHealth app in addition to standard of care phone communication (intervention group) or standard of care communication only (control group). In phase two, the prior collected data set will be used to develop machine learning algorithms to identify early markers of rejection, infection, and graft dysfunction posttransplantation. The primary outcome will be a composite of any unscheduled hospital admission, visits to the emergency department or transplant clinic, following discharge from the index admission. Secondary outcomes will include patient-reported outcomes using validated self-administered questionnaires, 1-year graft survival rate, 1-year patient survival rate, and the number of standard of care phone voice messages.

Results: At the time of this paper's completion, no results are available.

Conclusions: Building from previous work, this project will aim to leverage an innovative mHealth app to improve outcomes and reduce hospital readmission in adult solid organ transplant recipients. Additionally, the development of machine learning algorithms to better predict adverse health outcomes will allow for personalized medicine to tailor clinician-patient interactions and mitigate the health care burden of a growing patient population.

Trial Registration: ClinicalTrials.gov NCT04721288; https://www.clinicaltrials.gov/ct2/show/NCT04721288

International Registered Report Identifier (IRRID): PRR1-10.2196/26816

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KEYWORDS

mobile health; telemonitoring, transplantation; wearable sensors; solid organ transplant

Introduction

Solid organ transplant (SOT) is the standard therapy for select patients with severe end organ dysfunction. During the transition from pre- to posttransplant, recipients are introduced to a number of new medications and medical issues. In light of this complexity, early hospital readmission is common, ranging from 18% to 47% [1-3]. In addition to an increased burden on the health care system, early hospital readmission is associated with increased patient morbidity and mortality [4]. Although some readmissions are unpredictable and unavoidable, as many as half of early readmissions may be preventable [4].

Mobile health (mHealth) technologies such as smartphones and wearable devices hold promise to reduce hospitalization and improve patient outcomes through real-time monitoring, prompting timely clinician intervention that cannot be replicated in traditional outpatient care [5]. A recent systematic review showed mHealth apps improve patient self-management and reduce rates of rehospitalization in adults with cardiovascular disease [6]. Previous work from our group has shown that mHealth technology is safe, feasible, and associated with a 50% relative risk reduction in rehospitalization in adults with heart failure [7]. We anticipate that SOT recipients would also benefit from improved monitoring and removal of communication barriers as the most common reasons for readmission (eg, infection, rejection, elevated blood pressure, and metabolic derangements such as renal, glucose, and electrolyte abnormalities) and mortality may be mitigated by clinical intervention [1,2,5,8]. Additionally, medication adherence is critical in transplant patients to prevent graft rejection [9,10]. Enhanced and clear communication is likely to lead to improved patient outcomes.

Over the past decade, the number of SOTs in Canada has increased by 33% [11]. As transplant program volumes continue to grow, the need to reduce hospital readmissions is critical both for patients and to avoid straining the health care system. Building upon prior research in which the safety and feasibility of mHealth technologies in adult patients with heart transplants was demonstrated [12], larger scale clinical data is needed to determine whether this technology reduces hospital readmissions.

In the transplant population, it is likely that remote monitoring will improve medication adherence/adjustments and will allow for identification of early decompensation and reduce preventable hospital readmissions. Thus, this study will determine if an innovative mHealth intervention designed to improve patient-clinician communication reduces unnecessary hospital readmission and visits to the emergency department (ED) and transplant clinic when used in addition to the standard of care telephone communication system. We will also incorporate clinical and continuous ambulatory physiologic data collected as part of the mHealth intervention to develop machine learning (ML) algorithms capable of identifying early indicators of adverse outcomes in adult patients with heart, kidney, and liver transplants.

Therefore, we hypothesize that the delivery of personalized communication using an mHealth app will improve patient self-management, resulting in a reasonable reduction in preventable hospital readmission and unscheduled visits to the ED and transplant clinic of 50%. With tailored communication through the mHealth app, we expect fewer standard of care phone messages for patients in the intervention group, and patients with higher activity levels (average daily step count) pretransplantation will have lower index hospitalization length of stay. Finally, the large data set collected from this study will allow novel ML-derived risk prediction models to more accurately predict adverse outcomes (eg, organ rejection, infection, and death) compared to conventional regression models.

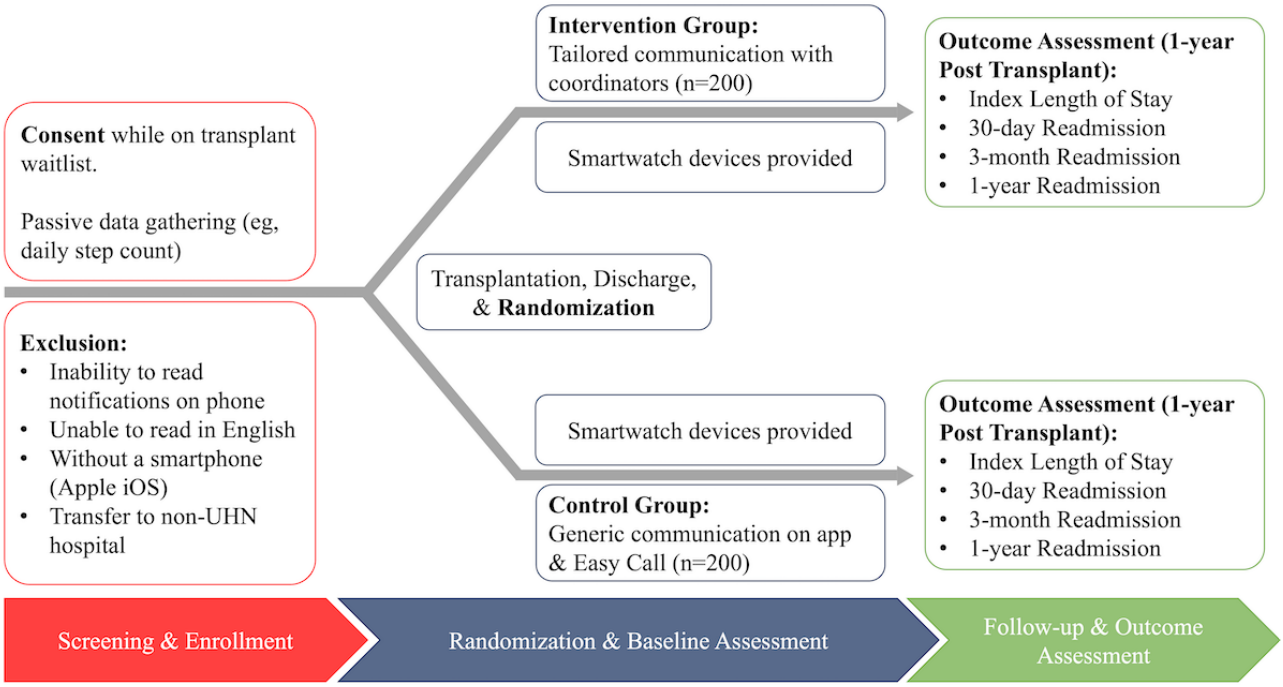
Methods

Overview

Remote Mobile Outpatient Monitoring in Transplant (Reboot) 2.0 is a registered (ClinicalTrials.gov NCT04721288) two-phased single-center study. It has also been approved by the University Health Network (UHN) Research Ethics Board (REB 20-6082.0.1). The first phase will consist of a 1-year concealed randomized controlled trial of 400 adult SOT (heart, kidney, or liver) recipients. Currently, the Ajmera Transplant Centre at the UHN (a large academic teaching site in Toronto, Canada) uses paper medical administration records to alter immunosuppressive medications, and patients generally record their vitals by pen and paper, both of which may be error prone. Additionally, health care providers and patients with transplants rely on a telephone-based (“Easy Call”) method of communication, wherein patients leave a message for their health provider when issues arise. The integration of medication and vitals tracking, as well as patient-provider communication into a single mHealth app may decrease errors and improve patient outcomes. To test this, participants will be randomized

to receive either personalized communication using an mHealth app in addition to the Easy Call system (intervention group) or Easy Call standard of care (control group; see Figure 1). In the second phase of Reboot 2.0, the data set from the 400 patients with SOTs collected as part of phase one will be evaluated in an attempt to identify early markers of rejection, infection, and graft dysfunction posttransplant.

Figure 1. Proposed study flowchart. UHN: University Health Network.



Participants

The UHN in Toronto, Canada conducted over 700 transplants in 2019, including approximately 225 liver transplants, 225 kidney transplants, and 40 heart transplants. Based on this distribution, we expect to recruit 150 to 200 liver transplant, 150 to 200 kidney transplant, and 40 to 50 heart transplant recipients from the SOT waiting list at the UHN. Inclusion criteria include heart, kidney, or liver transplant recipients; age ≥21 years; the ability to use a smartphone (Apple iOS); and English speaking. Exclusion criteria include patients with poor health literacy (defined as a reading level less than grade 5), transfer to a non-UHN hospital for follow-up and management, and an inability to follow instructions from the mHealth app.

Screening and Recruitment

Patients on the UHN transplant waiting list will be screened by study personnel for participation in this study. Consent and enrollment will be completed while participants are still on the transplant waiting list. Prior to discharge from the index hospitalization, patients will be randomized to either the intervention or control group. All patients will be given an Apple Watch at the time of discharge from their index hospitalization to record continuous ambulatory physiologic data. The use of smartwatch technology will allow autonomous step count tracking and rapid clinician intervention in response to patient inactivity, heart rate monitoring, heart rate variability, intermittent electrocardiography, and the development of robust ambulatory physiologic data that can power predictive ML algorithms for adverse patient outcomes.

Randomization

Concealment of allocation will be ensured by the use of a centralized 24-hour internet-based computerized randomization system. Participant will be the unit of randomization, and to protect against imbalance in known prognostic factors between groups, stratified randomization will be used. Stratification will be based on age (ie, 18-31 years, 31-50 years, or >50 years of age), organ transplanted (ie, heart, kidney, or liver), listing status (ie, urgent transplant or nonurgent transplant), and history of organ replacement therapy (ie, left ventricular assist device or dialysis). Block randomization, using four blocks, will ensure balance between participants randomized to the intervention and control groups.

Intervention

Both groups will have access to the Reboot 2.0 mHealth app and receive generic notifications (eg, for achieving a daily step goal) as well as the option to log vital signs (eg, blood pressure, heart rate, weight, and temperature); however, only participants in the intervention group will receive tailored communication. This aspect of the intervention is designed to improve patient care by providing organ-specific educational material, a medication list, and weekly updates on fitness status (eg, heart rate and step count) with the overall goal of improving patient self-care and management. This will also be supported through the delivery of personalized notifications (eg, app use incentives, appointment reminders, medication changes, and clinical care updates) through the app. The use of reminder notifications and the smartphone calendar will help avoid missed tests and appointments in the intervention group. More importantly, the intervention group will have access to active communication

with the transplant care team, including the ability to send asynchronous messages for nonurgent issues. Asynchronous messaging will be available as an integrated function within the mHealth app, accessible by the patient on their smartphone device and by the care team through the app's provider dashboard. The care team will respond to messages within 48 hours (the same time frame as the standard of care system) and copy message conversations from the provider dashboard to the electronic medical record, avoiding the need for verbal message transcription. This will reduce the need for patients and clinicians to leave messages on the standard of care system and therefore improve patient-provider communication. We expect that improving patient education and self-management, and alleviating communication barriers will facilitate earlier recognition of decompensation and avoid preventable hospitalizations and ED visits.

Standard of Care (Easy Call System)

Easy Call is the standard of care in the Ajmera Transplant Program within the UHN. This system allows transplant health care providers to leave messages for the patients regarding changes in their medication and appointment reminders. Patients, in turn, can also leave messages for health care providers should they require further clarification on their care. The Easy Call system will be available to both arms of this study.

Outcomes

The primary outcome for this study will be any unscheduled hospital admission or ED and unscheduled transplant clinic visit post discharge from the index admission during which the patients received their organ transplant. Readmissions and unscheduled ED/transplant clinic visits will be captured at 30 days, 3 months, and 1 year after organ transplant. A Central Adjudication Committee (CAC) composed of two transplant physicians from each organ group (ie, heart, kidney, and liver) will review each reported readmission to determine if they are study events and the most responsible diagnosis for readmission. Secondary outcomes will be assessed to capture participant illness experience and further quantify between-group differences in recovery from index transplantation. These will include patient-reported outcomes using validated self-administered questionnaires (see next section), 1-year graft survival rate, 1-year patient survival rate, number of Easy Call interactions, and index length of stay compared to pretransplant activity level (ie, step count). The CAC will also review all reported secondary outcomes and cases of graft loss or patient death to adjudicate the cause. Any disagreements within the CAC will be resolved by consensus.

Patient-Reported Outcomes

A health outcomes questionnaire (EQ-5D) and the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scale will be used to assess patient-reported outcomes. The EQ-5D is a comprehensive, compact health status classification and health state preference system. This questionnaire is widely used and has demonstrated validity and sensitivity in many populations [13-15]. PROMIS is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and individuals living with chronic conditions [16,17]. Both the EQ-5D and PROMIS questionnaires will be completed by participants at minimum 30 days, 3 months, and 1 year after SOT.

Study Follow-up

All participants will be followed at set intervals (approximately 30 days, 3 months, and 1 year from transplant), with participant health status and outcomes recorded at each point. A 1-year follow-up period was chosen as the study period as most patient challenges occur in the first year following transplant [8]. This time frame is the period of maximal benefit to patients and care providers when we anticipate the majority of unplanned but potentially avoidable readmission occurring.

ML Approach

Clinical and physiologic data captured in phase one will be continuously streamed from the Reboot 2.0 mHealth app on each participant's smartphone to Pattern Health's centralized secure server hosted by Amazon Web Services in the United States. This centralized data lake will be used to develop ML algorithms in the second phase of the study to better interpret raw patient data. Phase one data will consist of routine clinical data taken at baseline and regular follow-up appointments including demographics, comorbidities (eg, chronic kidney disease, diabetes, hypertension, obesity, and longitudinal changes in weight over time), metabolic scale body measurements, and laboratory and imaging investigations; ambulatory physiologic data collected via the Apple Watch (eg, vital signs and activity level); and laboratory and test results entered into the mHealth app (eg, blood glucose measurement or insulin administration). Additionally, details regarding the immunosuppression regimen used and longitudinal changes made will be incorporated. Some episodes of rejection, particularly in patients with liver transplants, may be managed as an outpatient, resulting in modifications to the immunosuppression regimen over time. Medications used for treatment of comorbidities (eg, diabetes, hypertension, or viral hepatitis) will also be taken into consideration (see Multimedia Appendix 1). These data will be automatically streamed into the centralized data lake (in the case of Apple Watch and patient-reported data) or extracted from the participant's medical record.

Categorical measurements (eg, gender) will be one-hot encoded [18] prior to normalization and temporal adjustment. Specifically, all participant demographic variables will be independently normalized to have mean zero and SD of one. Each feature with missing values will have a corresponding binary variable added denoting if the variable was observed or not. EQ-5D data will be coded into the five dimensions of health as five distinct features for analysis and following established guidelines for normalization [19]. The PROMIS Global Health scale will be coded using a similar approach. All other variables will be independently normalized to have a mean of 0 and an SD of 1. Measurement of mean, SD, maximum, and minimums will be recorded over fixed intervals, and the number of most recent intervals precluding an event will be included in the model (eg, the average heart rate per 3-day window taken over 12 days yields 4 distinct measurements). Missing measurements

will be counted per interval as an additional feature. For each patient window, this will create a fixed length feature variable that can be directly included and compared across the statistical and ML models. The interval width and number of intervals will be determined experimentally within the training data set. Following data processing, self-normalizing neural network [20], long short-term memory [21], random forest model [22], and extreme gradient boosted decision tree [23] approaches will be applied on a training portion of the data set to assess risk factors for the development of transplant outcomes. Early ML models will support the development of a ranked features list of clinically relevant variables, which will be used to inform subsequent model development.

The accuracy of each model (discrimination and calibration) and their relative performance (net-reclassification index) will be assessed in a portion of the data set reserved for testing. The development of predictive ML algorithms for adverse patient outcomes will allow for future personalized posttransplant medicine and early clinical intervention based on patient-specific data.

Statistics

Currently at the UHN, approximately 20% of patients are readmitted to the hospital within 30 days post SOT. In general, these patients are readmitted following presentation to either the ambulatory transplant clinic or ED. Although we do not have data on the number of patients that present to the ambulatory transplant clinic within 30 days post SOT, previous work has shown ED visits at 30 days to vary greatly between SOT groups (eg, as low as 17% for patients with kidney transplants, and as high as 44% for patients with liver transplants) [24,25]. Given this variability, we hypothesized a conservative estimate of 20% for our 30-day composite end point. To observe a 50% relative risk reduction, from 20% to 10%, for the 30-day composite end point, at an alpha of .05 and power of 0.8, 199 participants will need to be recruited for each group.

We will evaluate all outcomes using the intention-to-treat analytical approach. A Cox proportional hazard model will be used to evaluate the effect of the mHealth app on posttransplant unplanned readmission and ED and unscheduled transplant clinic visit rates (primary outcome). Results of this analysis will be reported as hazard ratios with 95% CIs. Kaplan-Meier curves will be used to depict freedom from unplanned readmission. Subsequent to running the Cox proportional hazard model, a logistic regression model will be used to analyze unplanned readmission rates at the prespecified time points of 30 days, 3 months, and 1 year. Results of the logistic regression model will be reported using odds ratios and 95% CIs.

Generalized linear models to estimate the mean difference in the intervention compared to the control group will be used to estimate the impact of personalized communication through the mHealth app on posttransplant patient-reported outcomes (secondary outcomes).

To avoid spuriously inflated estimates of treatment effect, an interim analysis will be conducted when 50% of participants are enrolled and have completed follow-up. The results of this analysis will be reviewed by an independent data monitoring committee. The O'Brien-Fleming stopping rule will be used based on our primary outcome and requires a $P \leq .007$ [26]. This conservative rule will avoid premature trial termination unless a large treatment effect is observed.

Results

Participant enrollment is expected to begin mid-2021. Data collection is anticipated to be completed by late 2023. At the time of this paper's completion, no results are available.

Discussion

Reboot 2.0 will build on previous pilot work that demonstrated the safety and feasibility of an mHealth intervention in adult patients with heart transplants [12]. It will be the first study to examine the clinical impact of this mHealth app on a large group (n=400) of diverse (heart, kidney, and liver) SOT recipients. In particular, the clinical trial phase of this research project will determine if leveraging an innovative and patient-centric mHealth app and smartwatch technology reduces hospital readmission and improves patient-reported outcomes as well as patient and graft survival in this population. If so, the mHealth app may be mobilized on a larger scale to reduce the burden on the health care system of a growing patient population. The results of this phase may be limited by its single-center design; however, the Ajmera Transplant Centre at the UHN is the largest in North America and therefore will allow for a diverse and representative participant population.

Phase two of Reboot 2.0 is particularly novel in that it will result in the development of a data registry from 1 year of clinical data, patient-reported data collected through the mHealth app, and ambulatory physiologic monitoring using the Apple Watch from 400 patients with SOTs. This will allow us to develop predictive ML algorithms to better predict adverse health outcomes in these patients, and the subsequent application of these algorithms will allow for more personalized transplant medicine and tailored clinician-patient interactions.

Acknowledgments

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Conflicts of Interest

EB is the CEO of Pattern Health. All other authors have no conflicts related to this project to disclose.

Multimedia Appendix 1
Summary of study measurements to be used in machine learning model development.
[DOCX File , 12 KB - resprot_v10i10e26816_app1.docx]

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Abbreviations

CAC: Central Adjudication Committee
ED: emergency department
mHealth: mobile health
ML: machine learning
PROMIS: Patient-Reported Outcomes Measurement Information System
Reboot: Remote Mobile Outpatient Monitoring in Transplant
SOT: solid organ transplant
UHN: University Health Network

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Protocol

A Behavioral Economics–Electronic Health Record Module to Promote Appropriate Diabetes Management in Older Adults: Protocol for a Pragmatic Cluster Randomized Controlled Trial

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Abstract

Background: The integration of behavioral economics (BE) principles and electronic health records (EHRs) using clinical decision support (CDS) tools is a novel approach to improving health outcomes. Meanwhile, the American Geriatrics Society has created the Choosing Wisely (CW) initiative to promote less aggressive glycemic targets and reduction in pharmacologic therapy in older adults with type 2 diabetes mellitus. To date, few studies have shown the effectiveness of combined BE and EHR approaches for managing chronic conditions, and none have addressed guideline-driven deprescribing specifically in type 2 diabetes. We previously conducted a pilot study aimed at promoting appropriate CW guideline adherence using BE nudges and EHRs embedded within CDS tools at 5 clinics within the New York University Langone Health (NYULH) system. The BE-EHR module intervention was tested for usability, adoption, and early effectiveness. Preliminary results suggested a modest improvement of 5.1% in CW compliance.

Objective: This paper presents the protocol for a study that will investigate the effectiveness of a BE-EHR module intervention that leverages BE nudges with EHR technology and CDS tools to reduce overtreatment of type 2 diabetes in adults aged 76 years and older, per the CW guideline.

Methods: A pragmatic, investigator-blind, cluster randomized controlled trial was designed to evaluate the BE-EHR module. A total of 66 NYULH clinics will be randomized 1:1 to receive for 18 months either (1) a 6-component BE-EHR module intervention + standard care within the NYULH EHR, or (2) standard care only. The intervention will be administered to clinicians during any patient encounter (eg, in person, telemedicine, medication refill, etc). The primary outcome will be patient-level CW compliance. Secondary outcomes will measure the frequency of intervention component firings within the NYULH EHR, and provider utilization and interaction with the BE-EHR module components.

Results: Study recruitment commenced on December 7, 2020, with the activation of all 6 BE-EHR components in the NYULH EHR.

Conclusions: This study will test the effectiveness of a previously developed, iteratively refined, user-tested, and pilot-tested BE-EHR module aimed at providing appropriate diabetes care to elderly adults, compared to usual care via a cluster randomized controlled trial. This innovative research will be the first pragmatic randomized controlled trial to use BE principles embedded within the EHR and delivered using CDS tools to specifically promote CW guideline adherence in type 2 diabetes. The study will also collect valuable information on clinician workflow and interaction with the BE-EHR module, guiding future research

in optimizing the timely delivery of BE nudges within CDS tools. This work will address the effectiveness of BE-inspired interventions in diabetes and chronic disease management.

Trial Registration: ClinicalTrials.gov NCT04181307; https://clinicaltrials.gov/ct2/show/NCT04181307

International Registered Report Identifier (IRRID): DERR1-10.2196/28723

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KEYWORDS

diabetes; behavioral economics; electronic health records; clinical decision support; randomized controlled trial; pragmatic

Introduction

Background

Behavioral economics (BE) is a field that combines the disciplines of psychology and economics to provide insight into how humans often fail to behave as perfectly rational agents [1-10]. The challenges for individuals of carefully weighing the costs and benefits in decision-making and arriving at optimal choices can be described via a variety of BE principles. A nudge is a BE-based tool that seeks to provide positive reinforcement and influence the behavior and decision-making of individuals or groups. Nudges are implemented in a variety of contexts, and their recent application in medicine to improve health outcomes has grown in popularity [11-17].

The specific system used to deliver nudges, as well as the environment in which they are deployed, will ultimately influence their success in improving health outcomes. One potential mode for nudge delivery is via electronic health record (EHR) technology. Clinicians interact daily with EHRs, which guide nearly all aspects of clinical care, including documentation, ordering, data review, and communication. Furthermore, providers may interact with clinical decision support (CDS) tools when accessing patient EHRs; these tools provide alerts and suggestions and redirect clinical behavior. EHRs and CDS tools therefore serve as an ideal platform for delivering nudges designed to influence clinician behavior, leading to improved patient care [18-22].

While the delivery of nudges through EHR and CDS tools shows great promise, the specific disease subtypes and environments in which nudges are most effective at influencing clinician behavior and subsequent patient health outcomes have yet to be determined. Nudges embedded within the EHR have been shown to improve processes of care, including reducing the rate of inappropriate antibiotic prescriptions for acute respiratory infections [13], increasing influenza vaccination rates [23], encouraging completion of high-value cancer screening tests [24], and increasing guideline-concordant statin prescribing [25]. There is, however, limited evidence supporting the effectiveness of nudges to positively influence chronic disease management, especially among older adults with type 2 diabetes mellitus.

Choosing Wisely (CW) is an American Board of Internal Medicine initiative to identify unnecessary tests, treatments, and procedures [26]. The American Geriatrics Society released 10 guidelines in 2013 (revised in 2015), the third of which promotes less aggressive glycemic targets and reduction in pharmacologic therapy for older adults with type 2 diabetes [27-29]. Providers may be unaware of these guidelines, resulting in excessive glycemic indices in older adults [30].

Herein, we describe the design of a pragmatic, cluster randomized controlled trial to test the effectiveness of a toolbox of nudges embedded within the EHR and utilizing CDS tools to promote appropriate diabetes management in older adults (ClinicalTrials.gov identifier: NCT04181307). Specifically, the behavioral economics–electronic health record (BE-EHR) intervention aims to reduce the overtreatment of older adults with diabetes per the CW guideline. The proposed study seeks to test the effectiveness of the newly developed, user-tested, refined, and previously pilot-tested BE-EHR intervention at promoting appropriate diabetes management in older adults.

Prior Work

We conducted a pilot study of the BE-EHR module intervention (ClinicalTrials.gov identifier: NCT03409523) in 5 clinics across the New York University Langone Health (NYULH) system [31]. The BE-EHR module consists of 6 nudge components, 2 of which were launched in 2 NYULH sites from June 12, 2018, until October 23, 2018, 4 (including the first 2 nudges) were launched in 5 American Geriatrics Society sites on October 24, 2018, and the 2 nudges each deployed on December 10, 2018, and April 8, 2019, respectively. All nudges were active in the NYULH EHR system, Epic (Epic Systems Corporation), through October 22, 2019. Despite the 6 BE-EHR components being introduced at varying time points across an approximately 10-month interval, we observed a 5.1% increase in CW compliance rates between the 16-week interval just prior to the launch of the first 2 nudges and the final 16 weeks of the pilot study [31].

Interpretation of the pilot study results, however, was limited. First, the intervention was launched in only 5 practices that were not selected at random. Second, due to the deployment of the nudges over an approximately 10-month period, all 6 BE-EHR components were active simultaneously for approximately 6 months, making the long-term effects of the entire intervention toolbox difficult to observe. Finally, only ~71% of the patient population had a return visit or new HbA_{1c} (hemoglobin A_{1c}) lab test at least 90 days after an initial test, suggesting that changes in CW compliance were not measurable in almost one-third of the study participants.

Thus, while the pilot study was successful in the development, user testing, and implementation of the BE-EHR module within the NYULH EHR system, a full-scale, sufficiently powered randomized controlled trial of longer duration is necessary to

estimate the effectiveness of the intervention at reducing the overtreatment of older adults with type 2 diabetes.

Methods

Setting

The cluster randomized controlled trial will be conducted in NYULH primary care and endocrinology clinics, which span the greater New York City area and include 2 sites in Florida. The NYULH system provides an ideal setting for this pragmatic study design due to its diverse patient sociodemographics and large population of older patients. Patient inclusion and administration of the intervention will occur using the NYULH EHR system, Epic. The study was approved by the Institutional Review Board at NYULH.

Eligibility Criteria

Study inclusion criteria require patients to be aged ≥76 years with type 2 diabetes as defined on the patient's "problem list" or "encounter diagnosis" within the EHR. Exclusion criteria include not taking medication to treat diabetes, an allergy to the medication metformin, and an estimated glomerular filtration rate of <30.

Randomization

The study will randomize 66 eligible clinics to 1 of 2 groups: (1) BE-EHR module + standard care or (2) standard care only. Clinics eligible for randomization must be active Epic users and have had at least 1 patient encounter in the year prior for which the above patient eligibility criteria were met.

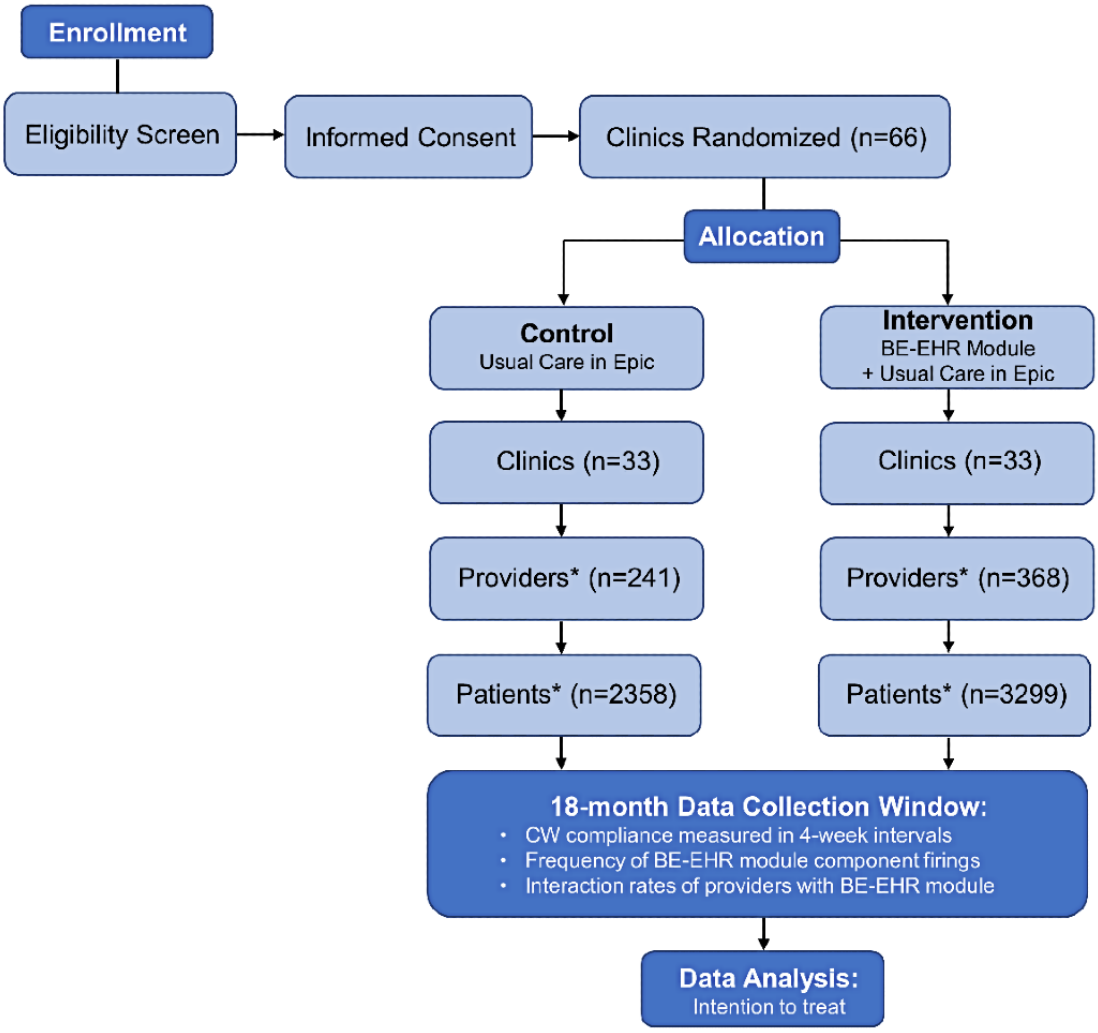
We conducted stratified randomization to ensure balance with respect to practice size and location. Practice size was measured by counting the number of eligible patients with an encounter at each NYULH site in 2019. The median number of eligible patients seen at each of the randomization-eligible practices in 2019 was 57 patients per site. Randomization was therefore stratified by clinics with fewer than or equal to 57 eligible patients in 2019 or greater than 57 eligible patients in 2019. Sites were also stratified by location into 1 of 2 groups: (1) practices located within Manhattan or Brooklyn or (2) practices outside of these 2 New York City boroughs. Randomization assignments according to this plan were generated by an unblinded study statistician using the software R v3.6.3 (The R Foundation for Statistical Computing) [32].

Study Design and Enrollment

The study design is a pragmatic, investigator-blind, cluster randomized controlled trial. A total of 66 NYULH clinics were randomized 1:1 to receive either a 6-component BE-EHR module + standard care intervention or standard care only (control) for a duration of 18 months. The study design is unique in that clinicians rather than patients within each practice will receive the intervention through their interaction with the NYULH Epic system during any eligible patient encounter (eg, in person, telemedicine, lab order, prescription refill, etc). Individual patients were not recruited; rather, we obtained a waiver of consent from the NYULH Institutional Review Board, and patients of physicians at participating clinics who met eligibility criteria were included. Therefore, patients at all eligible primary care, family care, and endocrinology clinics within the NYULH system were automatically recruited and enrolled in the study (Figure 1).

Prior to randomization, eligible practices were identified, and site directors were informed of the study and offered the opportunity to ask questions and to opt out of participation. The study design is investigator-blind in that the principal investigators will be blinded to the assignment of clinics to either the intervention or control arm, and all interim analyses will be presented to the blinded study team labeled only as "arm 1" and "arm 2." Only the study statistician and the Medical Center Information Technology Epic data management team will be unblinded, as will the clinicians receiving intervention-based alerts while interacting with Epic during an eligible patient encounter. The Data and Safety Monitoring Board will also receive information specific to the intervention and control arms.

Figure 1. Flow chart of the study design. A total of 66 clinics across New York University Langone Health were randomized 1:1 to the behavioral economics–electronic health record (BE-EHR) module + standard care (intervention) or standard care only (control) after meeting eligibility criteria and informed consent requirements. *The number of providers and patients per arm is an initial estimate as of October 12, 2020, based on eligible patient-provider encounters from the prior 18 months. Due to the dynamic nature of the study being embedded within the EHR, we expect providers and patients to enter and leave the study over the 18-month duration window. CW: Choosing Wisely.



Intervention

Overview

The BE-EHR module intervention contains 6 components or "nudges," each leveraging principles grounded in BE theory. Each component was developed to interface with NYULH's EHR system. Providers at the 33 clinics randomized to the intervention arm will receive elements of the BE-EHR module either when activated during an eligible patient encounter or according to a monthly dissemination schedule.

To appropriately tailor the intervention to the patient population and reflect the CW guideline, we developed an algorithm to categorize patients into 1 of 3 life expectancy categories: low, medium, and high. The algorithm incorporated a patient's current age and gender, and used a weighted scoring approach for the number of chronic conditions [33,34], along with previously developed life expectancy tables from Medicare beneficiary data [35]. The full description of this algorithm can be found in the supplementary information provided by Belli et al [31]. This life expectancy algorithm was programmed into the NYULH EHR system to drive content firing based on a patient's life expectancy categorization.

Design and User Testing

We employed a pragmatic, user-centered approach to develop the 6 components of the BE-EHR module for implementation into the NYULH EHR [36,37]. Full details of the design and user testing of the intervention during the pilot study phase can be found in Belli et al [31]; briefly, this entailed semistructured interviews with key informants; two 2-hour design thinking workshops; and site visits to 2 of the 5 clinics, including in-person observation of clinician use and interaction with the module in a live clinical setting.

BE-EHR Module Components

A detailed description of each BE-EHR module component, including the BE principles utilized and which key aspects of the user testing and feedback aided in the design, is provided below. Corresponding visualizations of each nudge in Epic can be found in the supplementary materials of Belli et al [31].

Nudge 1: Tailored Advisory

The "tailored advisory" BE-EHR module component activates noninterruptively in Epic during a clinician-patient encounter for any CW-noncompliant patient. It consists of an alert window that describes appropriate treatment guidelines for older adults given the individual's life expectancy categorization. Although a response is not required, clinicians may interact with the alert by clicking the "Agree with recommendation. Action taken" button, or by selecting the "Clinically inappropriate. Please explain" option, with space for free-text comments. Clinicians may also choose to suppress future activations of the tailored advisory nudge for a particular patient for half a year (182.5 days) with either of these acknowledgments. The optional nature of the alert, as well as the ability to suppress future activations, resulted directly from the user-design process. The tailed advisory nudge utilizes BE principles, including framing [5,38], social norming [39], suggesting alternatives [5], affirmation [40,41], emotional appeal [42], and accountable justification [43-45].

Nudge 2: Refill Protocol

The "refill protocol" is an alert window that appears in the refills section of Epic whenever a refill for diabetes medication is generated for study-eligible older adults. The alert suggests that providers order metformin as an alternative for patients who are not already taking the medication, or to consider refilling at a lower dose or not at all for patients who are already taking metformin. The provider may leave comments, but this is not required. During the user-testing phase, clinicians preferred the ability to leave comments as an optional action. The refill protocol nudge utilizes BE principles, including framing [5,38], social norming [39], suggesting alternatives [5], affirmation [40,41], emotional appeal [42], and accountable justification [43-45].

Nudge 3: Preference List

The "preference list" is implemented at the system level by providing an automatic default list, with metformin displayed at the top of the list of medications for "First-line Type 2 Diabetes." Orders for nonmetformin medications are not restricted, which was in line with clinician preferences during user testing. This nudge uses the BE defaults principle [14,46-48].

Nudge 4: Lab Result

The "lab result" nudge is an alert window that appears in the lab results section describing appropriate treatment guidelines for older adults whenever there is a new HbA_{1c} lab result for a CW-noncompliant patient. Features of the design, including the red text for those patients out of range and tabular formatting, resulted from the user-testing feedback. The alert remains active for 7 days following the result in Epic. BE principles utilized include framing [5,38], social norming [39], suggesting alternatives [5], and emotional appeal [42].

Nudge 5: Peer Comparison

The "peer comparison" nudge is the first of 2 nudges sent outside of the Epic system. Once per month, the peer comparison nudge is sent via a secured Microsoft Outlook account with the email subject line: "Message from the desk of Dr. [Insert Practice Director Name]." The email content includes 3 graphics displaying (1) CW compliance for the individual provider, (2) CW compliance for the clinician's practice site, and (3) CW compliance across all NYULH practices. The provider then receives either a "negative" or "positive" version of the accompanying text, depending on whether the clinician's CW compliance rate is above or below the rate of their respective practice. The graphic design of this nudge and positive versus negative text versions were iteratively refined after feedback from both clinicians and health services researchers. The peer comparison nudge utilizes BE principles, including social norming [39] and peer comparisons [49].

Nudge 6: Campaign

The "campaign" is the second nudge to alert clinicians outside of the Epic system; it serves the goal of bringing awareness to the CW guideline. The campaign was developed through a series of design workshops that included clinicians, researchers, and health services experts; game show–themed prototypes emerged and were ultimately user tested. The final campaign toolkit included 3 game show–themed animations inspired by *The Price is Right*, *Jeopardy*, and *Who Wants to Be a Millionaire*, as well as a flashcard deck that quizzes physicians on CW best practices. There are multiple versions among each of the 4 campaign themes that vary according to the 3 life expectancy categories and information provided. Clinicians receive at random a version of a campaign theme every month. The campaign utilizes BE principles, including gamification and competition [49].

Data Collection and Study Outcomes

The primary study outcome will be patient-level CW compliance. To measure CW compliance, patients will first be categorized into 1 of 3 life expectancy groups:

1. High life expectancy: healthy older adults with a limited number of comorbidities and a life expectancy of >10 years; HbA_{1c} target range of 7%-7.5%
2. Medium life expectancy: older adults with a moderate number of comorbidities and a life expectancy of 3+ to 10 years; HbA_{1c} target range of 7.5%-8%
3. Low life expectancy: older adults with multiple comorbidities and a life expectancy of ≤3 years; HbA_{1c} target range of 8%-9%.

Per the CW guideline, patients within each of these life expectancy categorizations will then be categorized as either CW compliant or noncompliant depending on their measured HbA_{1c} relative to the target range within their respective life expectancy category.

The following set of equations measure CW compliance and noncompliance for each life expectancy category:

1. High life expectancy:
   - CW compliance = ratio of eligible patients with HbA_{1c} range: 
   - CW noncompliance = ratio of eligible patients with HbA_{1c} range: 
2. Medium life expectancy:

- CW compliance = ratio of eligible patients with HbA_{1c} range: 
- CW noncompliance = ratio of eligible patients with HbA_{1c} range: 

3. Low life expectancy:
   - CW compliance = ratio of eligible patients with HbA_{1c} range: 
   - CW noncompliance = ratio of eligible patients with HbA_{1c} range: 

Secondary study outcomes will include the frequency of activation rates of the individual BE-EHR module components longitudinally; provider interaction with each intervention component, measured by frequency of clicks and workflow sequences within the NYULH EHR system; and email read receipts from the peer comparison and campaign nudges.

Statistical Analysis

Power

We used data collected during the pilot phase to inform the power calculation for the full-scale randomized controlled trial. In that study, a moderate increase of 5.1% in CW compliance was detected [31]. We used data from the pilot phase to adequately power the randomized controlled trial to detect a similar reduction of approximately 5 percentage points in the rate of CW noncompliance. These data from the pilot phase suggested an intraclass correlation coefficient (a measure of the degree of additional correlation among providers within the same practice) of 0.01. With an average of 10 providers per practice site, this yields a design effect of 1.09. Using the available pilot data, and assuming a type I error rate of 0.05 for a 2-sided test, 66 eligible NYULH practices (33 per arm) will provide 93% power to detect an effect size of 0.1. This power calculation supports the evaluation of the effectiveness of the 6-component BE-EHR module intervention as a combined toolkit; to discern the effectiveness of individual nudges, a prohibitively large trial would be required. In addition, providers will often receive multiple nudges at various time points and in differing order, making the evaluation of the effectiveness of individual BE-EHR module components challenging.

Analytic Plan

We will begin all analyses with descriptive summary statistics and graphical displays of all variables. All analyses will be performed using the software R v3.6.3 [32].

The primary study outcome will be patient-level CW compliance, which will be modeled using a 3-level logistic mixed-effects model. A binary indicator of patient-level CW compliance will serve as the dependent variable. Treatment group, time, and the interaction of the 2 variables will serve as the primary fixed effects, where time will be measured using indicator variables for each 4-week interval. The model will also include a patient-level random effect, provider-level random effect, and practice-level random effect to account for patients seen by providers nested within clinics. Although randomization should obviate the need for adjustment, we will explore whether it is necessary to adjust for covariates, including gender, age, life expectancy category, and total number of patient visits, the latter of which may capture a potential dose-response effect of exposure to the intervention.

Secondary outcomes, including activation of each module component and provider interaction with the BE-EHR module within Epic, will be reported as frequency counts overall and stratified by gender, age, life expectancy, and use of metformin versus nonmetformin medications. We will also analyze any free-text comments provided within the accountable justification components of the tailored advisory and refill protocol nudges to look for patterns and any association with CW compliance.

We will furthermore look at CW compliance rates among patients whose providers only received a single nudge or particular combination of nudges. Although statistical power will likely be limited for these comparisons, this exploratory analysis will provide clues as to which individual BE-EHR components may be more or less effective at improving patient CW compliance and guide future research in this area.

Finally, safety information will be collected, including the frequency of in-patient hospitalizations, emergency department visits, and deaths across the control and intervention arms.

Results

We randomized a total of 66 practices, with 33 clinics in each arm. The breakdown of practices by strata is shown in Table 1.

All 6 BE-EHR module intervention components were activated in the NYULH EHR on December 7, 2020. The study will run for a duration of 18 months with a possibility for extension if patient clinic visit activity is affected by the COVID-19 pandemic. All final results will be disseminated via publications, conference proceedings, and presentations.

Table 1. Clinics randomized by location and number of eligible patients.

Location and sample size	Control (n=33), n (%)	Intervention (n=33), n (%)
Manhattan/Brooklyn, ≤57 patients	10 (30)	7 (21)
Manhattan/Brooklyn, >57 patients	7 (21)	6 (18)
Outside Manhattan/Brooklyn, ≤57 patients	6 (18)	9 (27)
Outside Manhattan/Brooklyn, >57 patients	10 (30)	11 (33)

Discussion

This study is a novel, pragmatic randomized controlled trial that incorporates BE nudges into the EHR and CDS tools to promote CW guideline adherence in a chronic condition, namely type 2 diabetes. The BE-EHR module was designed after an extensive literature review of studies that have utilized BE nudges to improve clinical outcomes. Design of the BE-EHR module also incorporated behavioral change theory models, as well as a variety of BE principles. The extensive user testing process that the interdisciplinary study team undertook led to the development of an intervention that aims to reduce cognitive load on physicians through seamless integration into the NYULH EHR system, while allowing physicians the opportunity to interact with various BE-EHR module components only if they choose. Examples include leaving comments, following links to additional material regarding the CW guideline, or receiving a list of CW-noncompliant patients with whom they have interacted during a clinical encounter in the past month.

Furthermore, this study is innovative in that it tests the use of BE nudges in promoting clinical deprescribing. The research is also unique in that the intervention targets clinicians rather than the patients themselves. Furthermore, studying a population of elderly patients who have been living with type 2 diabetes and other chronic conditions for potentially long durations poses an interesting behavioral change problem that the study team seeks to address using BE nudges within the EHR.

Limitations of the study include testing of the BE-EHR module as a whole rather than evaluating individual components. However, a toolbox of BE nudges has yet to be proven effective in the context of treating type 2 diabetes, making this study an important first step in understanding the effectiveness of BE nudges for promoting appropriate type 2 diabetes management and the potential of BE nudges to lead to positive clinical outcome among other chronic conditions. If effective, further work will evaluate which elements of the toolbox are most impactful.

Furthermore, the study team attempted to reduce alert fatigue via a user-centered design that incorporated feedback from clinicians to help minimize the burden of the alerts. Additionally, some of the alerts were passive or noninterruptive, thus reducing their contribution to alert fatigue [50]. However, we acknowledge that any clinician interaction with CDS tools and EHRs poses a threat of clinician burnout [51,52]. Hence, we measure the primary outcome of CW compliance longitudinally in 4-week increments to ultimately estimate the duration of the intervention's effectiveness.

A third limitation is that the CW guideline may evolve over time, especially with the recently demonstrated benefits of sodium/glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide 1 (GLP-1) for diabetes and cardiovascular diseases [53]. Fortunately, all 6 components of the BE-EHR module are highly adaptable to changing guidelines, as well as to other CDS tools outside of the NYULH EHR system.

Results will estimate the effectiveness of the BE-EHR module in improving CW compliance, as well as provide insight into clinician interaction with the BE-EHR module. This study will therefore not only provide answers to fundamental questions regarding the effectiveness of BE nudges at promoting appropriate diabetes management, but will also guide future research aimed at optimizing the timing and location of BE nudges within the EHR and CDS tools, and inform other chronic conditions for which administering BE nudges using digital health tools may lead to improved clinical outcomes.

Based on pilot study results [31], we hypothesize that the BE-EHR module will increase patient-level CW compliance. In addition to testing the effectiveness of the BE-EHR module at promoting appropriate diabetes management in older adults, this study will also yield results on provider interaction with the module. This valuable information will provide insights into the real-time clinical workflow while BE nudges are being activated, providing useful information about the visibility of BE nudges to providers.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH checklist (V1.6.1).
[PDF File (Adobe PDF File), 12253 KB - resprot_v10i10e28723_app1.pdf]

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Abbreviations

BE: behavioral economics
BE-EHR: behavioral economics–electronic health record
CDS: clinical decision support
CW: Choosing Wisely
EHR: electronic health record
NYULH: New York University Langone Health
SGLT2i: sodium/glucose cotransporter-2 inhibitors
GLP-1: glucagon-like peptide 1

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Protocol

Improving the Prognosis of Pancreatic Cancer Through Early Detection: Protocol for a Prospective Observational Study

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Abstract

Background: Pancreatic cancer is associated with high mortality and its rates of detection are very low; as such, the disease is typically diagnosed at an advanced stage. A number of risk factors for pancreatic cancer have been reported and may be used to identify individuals at high risk for the development of this disease.

Objective: The aim of this prospective, observational trial is to evaluate a scoring metric for systematic early detection of pancreatic cancer in Mie Prefecture, Japan.

Methods: Eligible patients aged 20 years and older will be referred from participating clinics in the Tsu City area to the Faculty of Medicine, Gastroenterology, and Hepatology at Mie University Graduate School, until September 30, 2022. Participants will undergo a detailed examination for pancreatic cancer. Data collection will include diagnostic and follow-up imaging data and disease staging information.

Results: The study was initiated in September 2020 and aims to recruit at least 150 patients in a 2-year period. Recruitment of patients is currently still underway. Final data analysis is expected to be complete by March 2025.

Conclusions: This study will provide insights into the feasibility of using a scoring system for the early detection of pancreatic cancer, thus potentially improving the survival outcomes of diagnosed patients.

Trial Registration: UMIN-CTR Clinical Trials Registry UMIN000041624; https://tinyurl.com/94tbbn3s

International Registered Report Identifier (IRRID): DERR1-10.2196/26898

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KEYWORDS

pancreatic cancer; prognosis; early diagnosis; risk factors; scoring system; referral

Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death in Japan, and the number of cases is increasing annually [1]. Prognosis for individuals diagnosed with pancreatic cancer is poor, with a 5-year survival rate of 7.9% reported for patients diagnosed between 2006 and 2009 [2]. Pancreatic ductal adenocarcinoma, referred to simply as pancreatic cancer hereafter, is among the most lethal forms of the disease, with an overall 5-year survival rate of approximately 5% [2]. The overwhelming majority of patients with pancreatic cancer present with locally advanced or distant metastatic disease (80%-85%), and only a minority of patients have surgically resectable tumors [3-5]. Following initial evaluation, only 15%-20% of patients undergo resection [6-8]. In many cases, symptoms manifest only when the cancer reaches an advanced stage, such that by the time it is detected, the cancer may be unresectable. Such late detection is among the main reasons for the poor prognosis of patients with pancreatic cancer.

The Japan Pancreatic Cancer Registry has reported 5-year survival rates of 85.8%, 68.7%, and 59.7% for patients with Stage 0, Ia, and Ib disease, respectively [9]. The 5-year survival rate of patients with pancreatic tumors <10 mm (TS1a) approaches 80.4% and that of patients with Union for International Cancer Control (UICC) Stage 0 is 85.8% [6-10]. Therefore, early detection, which enables multidisciplinary treatment including surgical resection, chemotherapy, and radiation therapy, is key to improving prognosis. However, in Japan, the proportion of cases detected at Stage 0, Ia, and Ib is only 1.7%, 4.1%, and 6.3%, respectively [9], indicating that rates of early detection remain low.

Risk factors for pancreatic cancer include family history, diabetes mellitus, chronic pancreatitis, complication of intraductal papillary mucinous neoplasm, smoking, and excessive alcohol intake [11], but an efficient system to detect patients from high-risk groups has not yet been established. A multicenter retrospective study of early stage pancreatic cancer in Japan indicated a role for screening in individuals without symptoms and demonstrated the importance of imaging modalities including computed tomography (CT), active endoscopic ultrasound (EUS), and magnetic resonance imaging (MRI) for identifying abnormalities warranting further investigation [12]. In a previous study, early detection of pancreatic cancer on a regional basis via cooperation between a regional core hospital and the medical association, using EUS and MRI for diagnostic purposes, was effective for detecting Stage 0 pancreatic cancer [13], and another regional study reported the effectiveness of a similar system [14]. Therefore, we aim to implement a system for the early detection of pancreatic cancer in a regional referral setting in Mie Prefecture, Japan.

We hypothesize that referral of subjects for further examinations based on a scoring metric that assesses the presence of known pancreatic cancer risk factors is a feasible strategy to improve rates of early identification of patients with pancreatic cancer compared with current diagnostic practices.

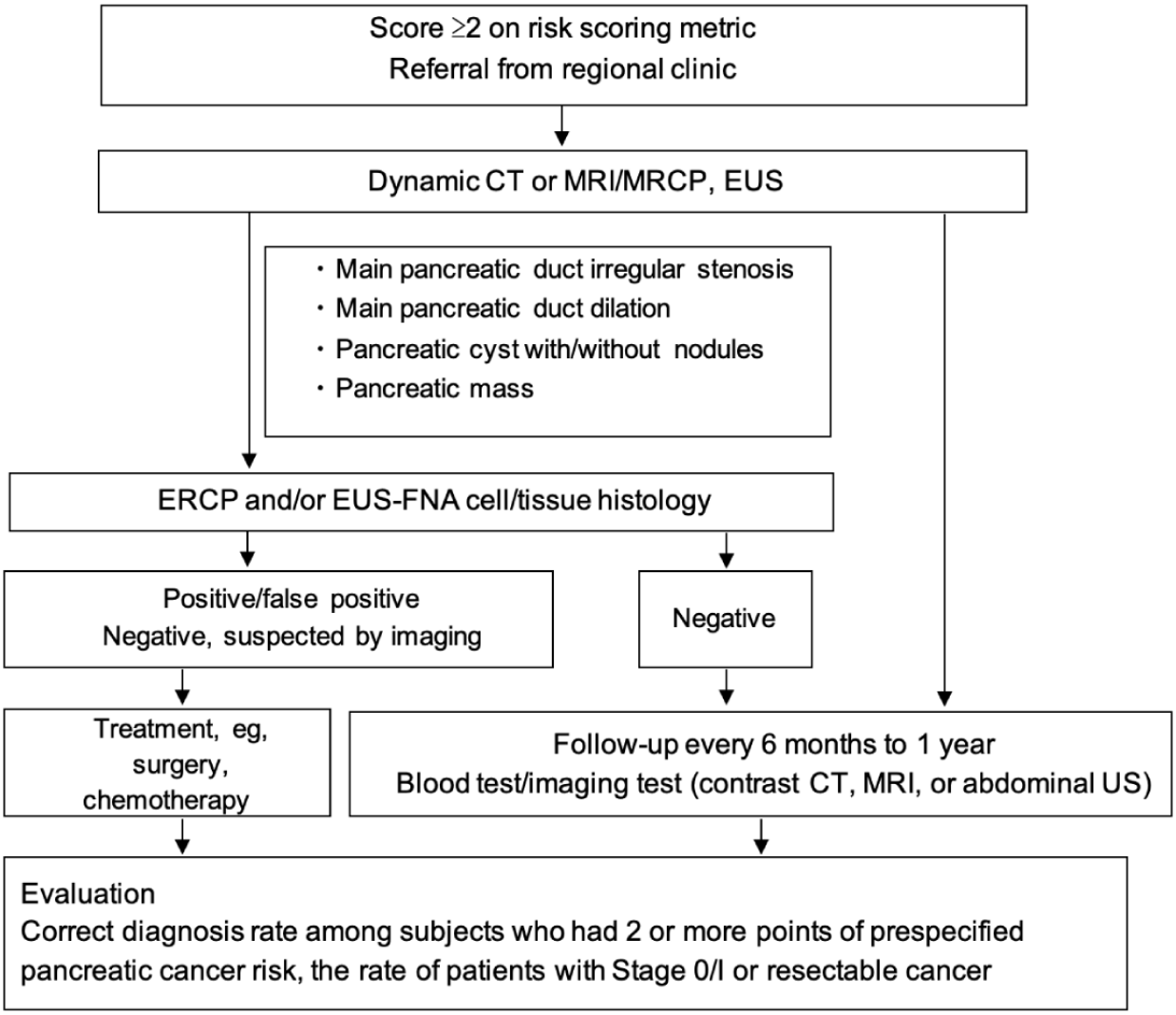
Methods

Study Design and Population

This is a prospective, multicenter, observational cohort study for the early detection of pancreatic cancer in Japanese patients. The study was initiated in September 2020 and aims to recruit at least 150 patients. The aim of the study is to assess whether using a scoring metric to screen for known pancreatic cancer risk factors will improve the rate of early identification in this patient population. The flowchart of patient enrolment and evaluation is summarized in Figure 1. The study is registered in UMIN-CTR Clinical Trials Registry (UMIN000041624). Patients who seek consultation at one of five participating local clinics in the Tsu City area until September 30, 2022, will be referred through the regional medical reference system to the Faculty of Medicine, Gastroenterology, and Hepatology at Mie University Graduate School for a detailed examination for pancreatic cancer.

Prespecified risk factors and associated point scores will be assessed as follows: symptoms (abdominal pain, jaundice, back pain, or weight loss): 1 point; newly diagnosed diabetes mellitus (type 2) or worsening of diabetes: 1 point; family history of pancreatic cancer (parent, child, or siblings, including other types of pancreatic neoplasms): 1 point; abnormal serum amylase level (under 44 U/mL or over 132 U/mL): 1 point; elevated serum CA19-9 level (>37 U/mL [15]): 1 point; pancreatic duct dilation (>3 mm) or pancreatic cyst detected by abdominal ultrasound: 2 points [11]. Adults aged 20 years or older scoring ≥2 points on this metric for prespecified pancreatic cancer risk factors will be eligible for inclusion (those scoring 2 or less but at high risk for pancreatic cancer will be referred for follow-up, but not included in the study). The total number of patients diagnosed with pancreatic cancer and the subsets of patients with surgically resectable pancreatic cancer and Stage 0/I pancreatic cancer will be determined (Figure 1). After registration, participants will undergo hospital visits every 6 months for a period of 2 years.

Figure 1. Flowchart of patient enrolment and evaluation. CT: computed tomography; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; US: ultrasound.



Diagnostic Procedures

Diagnostic data will be collected from patients referred to Mie University Graduate School of Medicine and will include the outcomes of routine EUS, dynamic CT, and MRI or magnetic resonance cholangiopancreatography assessments. Confirmatory diagnostic tests will include endoscopic retrograde cholangiopancreatography and endoscopic ultrasound-guided fine needle aspiration. Biopsy samples collected during EUS-FNAB will be fixed in alcohol and stained using the Papanicolaou multichromatic procedure. The remaining material will be fixed in 10% formalin and embedded in paraffin for cell block analysis to obtain histological diagnosis using hematoxylin and eosin staining. Tumor staging will be performed according to the UICC-American Joint Committee on Cancer tumor, node, and metastasis categories [16].

Follow-Up Assessments

Patients with a diagnosis of pancreatic cancer will undergo appropriate treatment (eg, surgery and/or chemotherapy) according to the standard of care guidelines [11]. Patients with negative diagnostic results will be followed by contract CT, abdominal ultrasound, and/or MRI. Blood testing for carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), amylase, and lipase will be performed at intervals of 6 months.

Study Endpoints

The primary endpoint is the diagnosis rate (number of patients diagnosed/total number of study participants) for pancreatic cancer, calculated with a 95% CI. The secondary endpoints include the diagnosis rates of pancreatic cancer by stage, pancreatic neoplasms other than pancreatic ductal adenocarcinoma, Stage 0/I pancreatic cancer at each visit, and surgical resection. For patients with a definite diagnosis of pancreatic cancer, a frequency table will be created based on the resectability classification [16].

Sample Size

We based our sample size on data from a previous study, in which 28 patients were diagnosed with pancreatic cancer among 224 subjects who had 2 or more pancreatic cancer risks [14]. The risks prespecified in this study are considered equivalent to those reported previously, meaning that the rate of the patients

diagnosed with pancreatic cancer is expected to be approximately 10%. To obtain estimation accuracy (95% CI) of ±5%, the required number of subjects is calculated as 138. The planned number of participants in this study is 150. We expect that approximately 100-150 patients with ≥2 points on the pancreatic cancer risk scoring metric will visit the participating clinics per year and that 80% of these eligible patients will give consent to participate in the study [14]. Therefore, in the 2-year referral period, 160-240 participants are expected to enroll in this study. However, when the number of patients reaches 150, registration will continue because this a prospective observational study without any intervention.

Statistical Analyses

Patient characteristics will be summarized using descriptive statistics with frequency, mean, and standard deviation. The following items will be evaluated: sex, age, symptoms suggestive of pancreatic cancer (abdominal pain, jaundice, back pain, and weight loss), newly diagnosed or worsening of type 2 diabetes, family history of pancreatic cancer, abnormal laboratory test value for serum amylase (high or low) or serum CA19-9 (high), pancreatic duct dilation, or pancreatic cyst detected by echography. Participants' BMI and smoking status will also be recorded for use in adjusted analyses.

Loss of participants to follow-up will be minimized by monitoring missed appointments and contacting participants promptly. Where key data items are unavailable or only partially reported, we will use multiple imputation to impute missing data where indicated.

Data on patients with a confirmed diagnosis will be summarized using descriptive statistics according to resectability classification [16]. Binomial logistic regression analysis (both univariate and multivariate analyses) will be performed with a diagnosis of pancreatic cancer as the objective variable and each risk factor and the result of an imaging test as explanatory variables. For the primary multivariable analysis, variables will be selected with a two-sided significance level of 5%. In addition to the unadjusted analyses, logistic regression analyses adjusted for BMI and smoking status will be conducted.

Sensitivity analysis will be conducted to generate multivariable prediction scores based on all available risk factors, regardless of performance or significance on univariable analysis, and based on alternate combinations of risk factors as indicated. Formal comparisons of the relative goodness-of-fit of each model will be conducted through derivation of the Akaike Information Criteria and/or the Bayesian Information Criteria as indicated. We will compare the performance of the prediction score based on this primary model against those of the sensitivity analysis models.

No interim analysis or subgroup analysis will be performed. A separate follow-up study will be conducted to evaluate the 5-year survival rate of pancreatic cancer in the region. SPSS statistical software (Version 25.0, IBM Corp) will be used for all analyses.

Ethical Approval and Informed Consent

This study protocol has been approved by the ethics committee of Mie University Graduate School of Medicine (approval number H2020-143). All participants will provide written informed consent prior to study enrolment.

Results

The study was initiated in September 2020 and aims to recruit at least 150 patients in a 2-year period. Recruitment of patients is currently still underway. Final data analysis is expected to be complete by March 2025.

Discussion

The detection of pancreatic cancer, particularly at the early stages when 5-year survival rates are relatively high, remains challenging. Despite advancement in the knowledge of potential risk factors that cause pancreatic cancer and newly available tools for early diagnosis, its incidence is increasing and is estimated to include 355,317 new cases per year up to 2040 [17]. Previous studies have revealed the value of using clinical findings to detect early pancreatic cancer [12-14]. Sakamoto et al [14] found that of the five clinical findings they investigated, three (symptoms, new onset diabetes, and high CA19-9) were more frequent in the advanced pancreatic cancer group than in the early and non–pancreatic cancer groups. In contrast, high amylase and/or high pancreatic amylase levels were significantly more frequent in the early pancreatic cancer group than in the other groups. Similarly, CA19-9 levels >37 U/mL had a sensitivity, with 95% specificity, of 68% and 53% for detecting pancreatic cancer at >1 year and >2 years before diagnosis, respectively [18].

We plan to initiate a prospective, observational study designed to evaluate a scoring metric for systematic early detection of pancreatic cancer in Mie Prefecture, Japan. If demonstrated to be effective, our system may represent a novel tool for use in the diagnosis and subsequent management of this patient population. A strength of our study is that, although patients will be referred from five different participating centers, all diagnostic and follow-up assessments will be performed at a single institution, eliminating variability in local practices. A possible limitation is that, for ethical reasons, this study will not directly compare the scoring metric with no scoring in terms of new diagnoses. However, the rates of diagnoses, particularly of early stage pancreatic cancer, can be compared with historic published data. Additionally, with a relatively small sample size, this initial study will be limited in its ability to be applied to the wider population and different ethnicities because most of the participants are likely to be Japanese. A planned future study will examine 5-year survival after referral using the scoring metric and the value of each item in the scoring metric for detecting early stage pancreatic cancer in a larger number of patients.

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Authors' Contributions

RY designed the model and computational framework and analyzed the data. SI, TK, YK, SM, and NW are principal investigators at each institution. TF provided a security framework for the information processing system. TO participated in the design of the study and performed the statistical analysis. ST participated in the design of the study and helped to draft the protocol. SM, MK, YM, AH, HI, YU, KT, YH, and JT participated in data acquisition. All authors discussed the results and commented on the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CA19-9: carbohydrate antigen 19-9
CEA: carcinoembryonic antigen
CT: computed tomography
EUS: endoscopic ultrasound
MRI: magnetic resonance imaging
UICC: Union for International Cancer Control

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Protocol

A New Tool for Safety Evaluation and a Combination of Measures for Efficacy Assessment of Cotransplanting Human Allogenic Neuronal Stem Cells and Mesenchymal Stem Cells for the Treatment of Parkinson Disease: Protocol for an Interventional Study

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Abstract

Background: Parkinson disease (PD) is a neurodegenerative disorder associated with a broad spectrum of motor and nonmotor symptoms. Any proposed cure needs to address the many aspects of the disease. Stem cell therapy may have potential in this regard as indicated in recent preclinical and clinical studies.

Objective: This protocol aims to examine the safety and therapeutic benefit of human Wharton jelly-derived mesenchymal stem cells (WJ-MSCs) and their derivatives, neuronal stem cells (NSCs) in PD.

Methods: This clinical trial is a double-arm, single-blinded, phase I-II interventional study. Participants have been allocated to 1 of 2 groups: one receiving allogeneic WJ-MSCs alone, the other receiving NSCs and WJ-MSCs. Participants are being followed-up and assessed over a period of 6 months. To assess safety, an incidence of treatment-emergent adverse events (TEAEs) tool tailored for PD is being used immediately and up to 6 months after treatment. For efficacy assessment, a number of factors are being used, including the gold standard severity test and the Unified Parkinson Disease Rating Scale. In addition, the following standardized assessments for different common symptoms in PD are being included: motor (both subjectively and objectively assessed with wearable sensors), sensory, quality of life and psychological well-being, cognition, and sleep quality. Furthermore, immune-modulatory cytokines and neuronal damage versus regeneration markers in PD, including the neuronal protein linked to PD, α-synuclein, are being monitored.

Results: Ten patients have been enrolled in this study and thus participant recruitment has been completed. The study status is active and beyond the recruiting stage. Study chart implementation, data collection, and analysis are ongoing.

Conclusions: The combination of NSCs and MSCs in PD may be useful for harnessing the best of the immunomodulation and neural repair characteristics of these cell types. The tailored comprehensive and scaled TEAEs and the variety of evaluation tools used enables a comprehensive assessment of this cellular therapy treatment protocol. A consideration of this expanded tool set is important in the design of future clinical studies for PD.

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International Registered Report Identifier (IRRID): DERR1-10.2196/29695

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KEYWORDS

Parkinson disease; neurodegenerative disease; regenerative medicine; mesenchymal stem cells; MSCs; neuronal stem cells; NSCs; Unified Parkinson Disease Rating Scale; UPDRS; Mobility Lab; α-synuclein; PARK-7; stem cells; stem cell therapy; therapeutics; Parkinson's; neurological diseases

Introduction

Parkinson disease (PD) is the most common movement disorder and the second most common neurodegenerative disorder of aging [1]. This neurodegenerative disease arises due to the loss of dopaminergic neurons of the substantia nigra pars compacta, a basal ganglia structure located in the midbrain that plays an important role in bodily movement. PD is commonly recognized through clinical motor signs of tremor, rigidity, and bradykinesia, with postural instability often appearing as the disease progresses. Nevertheless, PD is associated with a broad spectrum of nonmotor symptoms that habitually precede motor symptoms and that have been found to be associated with a reduced quality of life [2]. These signs include mood disorders, cognitive dysfunction, sensory dysfunction with hyposmia, and disturbances of sleep-wake cycle regulation [3].

Conventional treatment strategies for managing motor and nonmotor symptoms of PD have included medical and surgical methods. Medical therapy relies on replenishing dopaminergic activity in the basal ganglia, with levodopa being the pillar of the medical therapy. In addition, deep brain stimulation is the most common surgical procedure and is designed to mitigate the motor symptoms of PD by targeting the subthalamic nucleus and globus pallidus par interna [4]. Although these therapies are helpful in alleviating and halting the symptoms in many cases, some patients do not respond to these methods while others suffer their side effects. In levodopa-based medical therapy, the drug effect usually wears off after a short time as the disease progresses, requiring increased frequency of dosing [5]. Moreover, even though deep brain stimulation has been approved by the US Food and Drug Administration for PD treatment, its related adverse events are unpredictable [6]. They may include hardware-related complications leading to infection and stimulation-induced phenomena, such as paresthesia, dysarthria, ataxia, and hypotonia.

In recent years, regenerative medicine has been investigated in neurological diseases, including PD, with a clear potential being demonstrated but at varying efficacy levels. Several types of stem cells have been used in experimental studies related to PD, including embryonic pluripotent stem cells, mesenchymal stem cells (MSCs), and induced pluripotent stem cells. MSCs have been studied extensively and present several advantages over other types of stem cells. These include minimum manipulation, relatively high genetic stability, and ease of isolation and accessibility from various tissues, such as bone marrow, adipose tissue, and peripheral blood. The umbilical cord is the most accessible source of MSCs than can be used to generate large numbers of high proliferating human Wharton jelly-derived MSCs (WJ-MSCs) which can be stored in biobanks. MSCs have been found to be capable of replacing and rescuing degenerated dopaminergic and nondopaminergic neurons, suggesting its potential for the treatment of both motor and nonmotor symptoms of PD [7].

The multipotency characteristic of MSCs enables them to differentiate into many cell types, including neurons and other neuronal cells [8]. WJ-MSCs differentiated into neuronal stem cells (NSCs) were found to have enhanced therapeutic potential compared to WJ-MSCs. NSCs exhibit neuroectodermal characteristics with reduced capacity to undergo mesodermal differentiation while preserving their immune modulatory properties [9]. This means that NSCs are more committed to the neuroectodermal lineage with minimized risk of ectopic differentiation following central nervous system transplantation [10].

The safety and clinical outcome of using allogenic MSCs alone or alongside their derived NSCs in PD individuals have not yet been investigated. The available research on the safety and efficacy of therapeutic agents for PD is rarely comprehensive because not many aspects of the disease are examined, leading to an incomplete evaluation. Therefore, this study has been designed to assess and compare NSCs cotransplanted with MSCs to MSCs alone. The study's protocol aims to produce clear conclusions regarding the safety and the comparative benefits of both treatment arms in regard to the different aspects of life commonly affected by PD.

Methods

Ethical Approval and Recruitment

The study protocol was submitted to the Research Ethics Committee of the Cell Therapy Center (CTC) at the University of Jordan (approval #IRB/01/2018). All study procedures are following the ethical principles of the Helsinki declaration. Trained research personnel explained benefits and risks of participation in this study during the consent process, and all eligible participants signed an informed consent form. The study protocol is registered in the American Registry of Clinical Trials (NCT03684122).

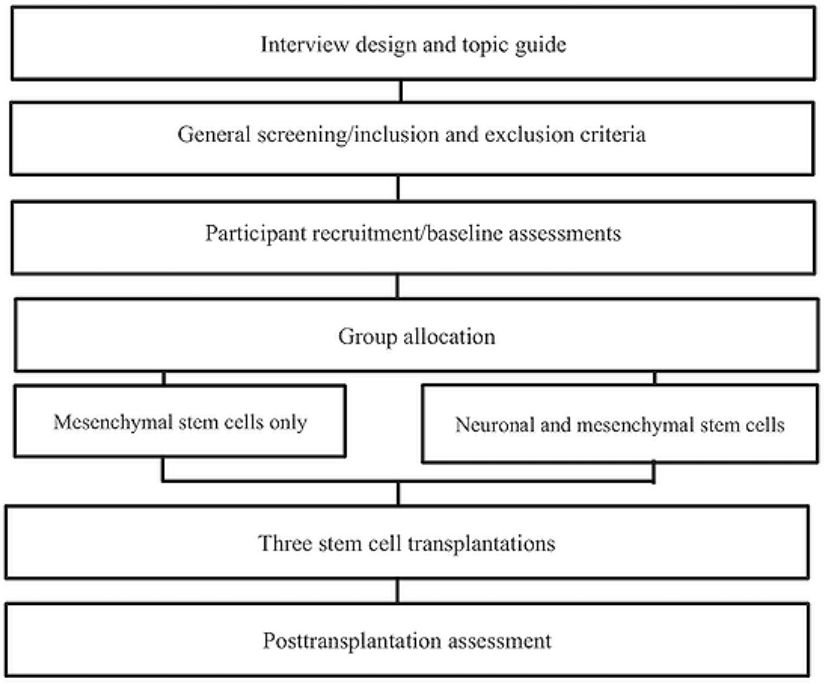
Potential participants were recruited using study flyers that were distributed in the neurology clinic at Jordan University Hospital, shared on different social media platforms and the CTC official website. Flyers included an invitation for interested people with PD to participate in the study, a brief explanation of the aims and design of the study, and contact numbers of study team members responsible for participants' recruitment. Subsequent phone interviews were conducted with interested individuals. Screening information collected included participant's profile, past medical history, current medication list, date of diagnosis

with PD, and current functional limitations. Consequently, participants were scheduled for their baseline assessment, in which they were considered as eligible or ineligible according to the predefined criteria regardless of gender, ethnicity, or social background.

Study Design

This study is a double-arm, single-blinded, phase I/-II interventional clinical trial. The protocol is designed to compare injecting MSCs and their derived NSCs to injecting MSCs alone. Ten participants with PD who matched the inclusion and exclusion criteria detailed in the next section were assigned into 1 of 2 arms. Participants in the 2 groups were matched based on age, gender, disease severity (according to the Hoehn and Yahr Scale) and Unified Parkinson Disease Rating Scale (UPDRS) scores. All participants are being assessed at 3 different time points: up to 1 week before first intervention, and at 3 months and 6 months after. The study design is summarized in Figure 1.

Figure 1. Study plan summarizing the different stages of the clinical trial.



The primary objective is to evaluate the safety of the cellular therapy protocols. Immediate, short-term, and up-to-6-month treatment-emergent adverse events (TEAEs) are being thoroughly examined. The secondary outcome includes the efficacy of both stem cell therapy protocols which will evaluated by documenting and correlating changes in motor and nonmotor functions, in addition to examining biological markers of inflammation and neural regeneration and repair.

Inclusion and Exclusion Criteria

Participants were required to meet the following inclusion criteria in order to be included in the study: nonsmoker; aged between 18 and 80 years; physician diagnosis of idiopathic PD confirmed from a medical file provided by participants; disease duration between 1 and 15 years; robust response to dopaminergic therapy (defined as greater than 33% reduction in symptoms on the UPDRS when measured in the “On medicine” state compared to the “Off medicine” state); for participants taking any central nervous system–related medications (eg, benzodiazepines, antidepressants, hypnotics), a regimen that is optimized and stable for 90 days prior to the screening visit; stable PD symptomatic therapy for at least 90 days prior to screening; for women of childbearing potential, a reliable form of contraception from 30 days prior to baseline visit until 6 months after treatment; and a clear infectious panel examination including hepatitis B and C, HIV, and syphilis.

Meanwhile, if participants met any of the following exclusion criteria, they were deemed ineligible to participate in the study: a typical or drug-induced Parkinsonism; a UPDRS rest tremor score of 3 or greater for any limb on medication; a Montreal Cognitive Assessment score of less than 25; clinical features of psychosis or refractory hallucinations, uncontrolled seizure disorder, defined as a seizure within the last 6 months; developmental delay; hepatic disease or altered liver function as defined by alanine transaminase >150 U/L and or T bilirubin >1.6 mg/dl at admission; history of congestive heart failure or clinically significant bradycardia and presence of second- or third- degree atrioventricular block; active malignancy or diagnosis of malignancy within 5 years prior to the start of screening (with cancer-free status for at least 5 years being permitted, and skin cancers, except for melanoma, being permitted); history of stroke or traumatic brain injury; major surgery within the previous 3 months or planned in the ensuing 6 months’ clinically significant abnormalities in the screening laboratory studies; history of use of an investigational drug

within 30 days prior to the screening visit; unable to return for follow-up visits for clinical evaluation and laboratory studies; and any other condition the investigator feels would pose a significant hazard to the participant if enrolled or that would complicate the study assessments.

Baseline Assessments

Participants were scheduled for an initial evaluation at the CTC, University of Jordan. Participants were then asked to fill and sign a consent form, which was explained thoroughly by research personnel. Thereafter, participants underwent a comprehensive battery of measures including motor and nonmotor medical assessments, which took approximately 3 hours to complete. By the end of the baseline assessment, it was determined whether a participant was eligible for inclusion or not. All participants deemed eligible were scheduled to undergo posttreatment assessments after 3 and 6 months.

Stem Cell Preparation

Human WJ-MSCs

Stem cell injections were prepared from thawed WJ-MSCs previously cryopreserved in the biobank of the CTC. Isolation of MSCs from healthy and bioscreened umbilical cord donor was performed according to good laboratory practice standard operation protocols. Characterization of the isolated stem cells was required to meet the defining criteria of MSCs, including microscopic spindle shape, surface marker expression, and trilineage differentiation, in accordance with the International Society for Cellular Therapy recommendations [11]. Briefly, the cord was rinsed with phosphate-buffered saline (PBS; pH 7.4) and cut into 5-cm-long pieces. The pieces were cut longitudinally, and the blood vessels were removed. The remaining tissues were cut into ~4 mm^2 pieces and plated in tissue culture plates. The explants were allowed to attach for about 15 minutes, and then culture medium was gently added to the plates and incubated without moving for 8 days.

The WJ-MSCs' expansion culture medium consisted of α-modified minimum essential medium (Thermo Fisher Scientific) supplemented with 5 % human platelet lysate, 1% (w/v) penicillin/streptomycin, and 2 mM of L-glutamine (Thermo Fisher Scientific).

Subsequently, culture medium was changed every 3 to 4 days, and cells were passaged at 80% confluence with xenogenic-free TrypLE 10X dissociation reagent (Thermo Fisher Scientific). Prior to cryopreservation, MSC batches were karyotyped to examine gross chromosomal aberrations. In addition, deep cytogenetic analysis was performed with Cytoscan microchips and ChAS software (Thermo Fisher Scientific).

The final cell suspensions, ranging from 80 to 120 × 10^6 MSCs, was prepared for intrathecal injection while another of 40 to 60 × 10^6 MSCs was prepared for intravenous injection in preservative-free normal saline. An automated cell counting instrument with disposable chambers was used to determine the number of cells administered (Thermo Fisher Scientific). The system identified cell viability and cell concentrations from 1 × 10^4 to 1 × 10^7 cells per milliliter with a mean diameter detection of 5 μm to 60 μm.

Human Neuronal Stem Cells

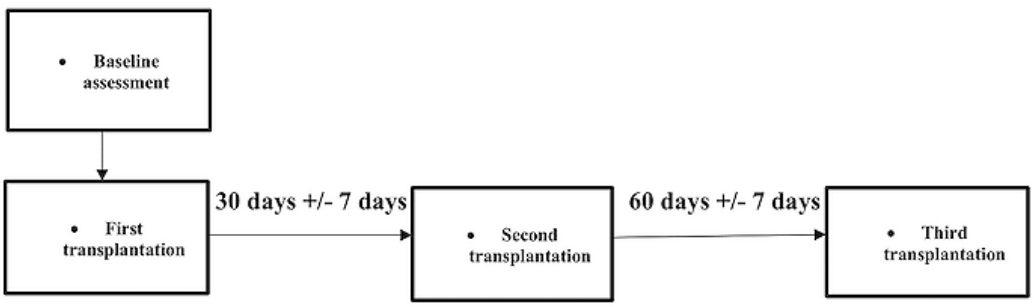
The same biological sample of umbilical cord–derived MSCs was used for NSC generation. WJ-MSCs were thawed and expanded for 4 days in low-adherence flasks. The differentiation culture medium was the Neurobasal Medium (Thermo Fisher Scientific) supplemented with 2% B27 growth factor (Thermo Fisher Scientific). Cells were harvested 8 to 12 days after differentiation. Floating "neurospheres" became visible in the culture after 2 to 5 days. Immunocytochemistry staining with nestin-2 and PAX-6 was performed for further characterization of neuronal differentiation. To obtain single-cell suspensions of NSCs, neurospheres were triturated in TrypLE (10×) with a serological pipette and then diluted with PBS (Thermo Fisher Scientific). NSC genetic stability was examined after DNA extraction (Qiagen) and compared to thawed MSCs using Cytoscan microchips and ChAS software (Thermo Fisher Scientific).

Prior to injection, cells were centrifuged, resuspended with PBS for counting and diluted to the final cell number between 8 and 12 × 10^6 NSCs per injection in preservative-free normal saline. Cells were delivered to the clinical unit in the CTC for immediate use.

Stem Cell Transplantation Protocol

Stem cell transplantation for each participant was held at the ICU rooms of the CTC clinical unit. Vital signs of each participant were monitored prior and throughout the procedure. The treatment protocol entails 3 consecutive injections: the first within a week of the baseline assessment, and the second and third 1 month and 3 months after, respectively (Figure 2).

Figure 2. Stem cell transplantation schedule.



At each time point, MSCs were intravenously delivered for all patients and either NSCs or MSCs were cotransplanted intrathecally. For intrathecal injections, 1 ml to 2 ml of 2% lidocaine hydrochloride solution, a local anesthetic agent, was used. Spine X-ray images were examined by the physician to take into consideration any anatomical variations. A disposable, sterilized epidural kit was used for every participant with appropriate long-needle size according to participant's weight. A volume of 5 ml to 10 ml of cerebrospinal fluid was aspirated and immediately frozen at –80 °C, followed by stem cell transplantation of a similar volume to limit central nervous system pressure with consequent headaches.

Treatment-Emergent Adverse Event Reporting

Preceding the intervention, vital signs measurements and extensive medical history with complete system review for enrolled participants were performed by trained nursing staff in the CTC.

Following the intervention, TEAEs were monitored and recorded according to the following schedule: immediate follow-up, 24-hour follow-up, 1-week follow-up, 1-month follow-up, and 3-month follow-up. Based on available TEAE assessment tools, a detailed scaled questionnaire was compiled specifically for this trial [12-14]. This enables a comprehensive assessment of any relevant symptoms that might appear after administration of a new treatment regimen for PD and is designed to be used for related neurological diseases (Table 1).

Table 1. Scaled incidence of treatment-emergent adverse event (TEAEs) reporting tool for immediate assessment.

Adverse effect	Grade				
	1	2	3	4	5
Allergy	Transient flushing or rash; drug fever <38 °C (<100.4 °F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38 °C (≥100.4 °F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema or angioedema; hypotension	Anaphylaxis	Death
Pain	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL[a]	Severe pain; pain or analgesics severely interfering with ADL	Disabling	N/A[b]
Injection site swelling	<2.5 cm	2.5-5 cm	>5 cm	N/A	N/A
Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA[c]	Severe and generalized erythroderma, macular, papular, or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Vasovagal episode	N/A	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with function, but not interfering with ADL	Disabling	N/A
Fever	38.0-39.0 °C (100.4-102.2 °F)	>39.0-40.0 °C (102.3-104.0 °F)	>40.0°C (>104.0 °F) for ≤24 hours	>40.0 °C (>104.0 °F) for >24 hours	Death
Palpitation	Present	Present with associated symptoms (eg, lightheadedness, shortness of breath)	N/A	N/A	N/A
Numbness	Mild symptoms	Mild symptoms	Severe symptoms; limiting self-care ADL	N/A	N/A
Speech impairment	N/A	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	N/A
Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	N/A
Muscle cramp/soreness	Mild pain	Moderate pain limiting instrumental activities of daily living	Severe pain limiting self-care activities of daily living	N/A	N/A
Seizures	N/A	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough of generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (eg, status epilepticus, intractable epilepsy)	Death
Fatigue	Mild fatigue over baseline	Moderate or causing difficulty in performing some ADL	Severe fatigue interfering with ADL	Disabling	N/A
Blurred vision	Symptomatic and not interfering with function	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Disabling	N/A
Sweating	Mild and occasional	Frequent or drenching	N/A	N/A	N/A
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	N/A	N/A
Blood with stool	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death

Adverse effect	Grade				
	1	2	3	4	5
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (eg, inadequate oral caloric and/or fluid intake); tube feeding or TPN[d] indicated	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	N/A	N/A
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours; IV[e] fluids indicated <24 hours	≥6 episodes in 24 hours; IV fluids or TPN indicated ≥24 hours	Life-threatening consequences	Death
Dry mouth	Symptomatic (eg, dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms: oral intake alterations (eg, copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1-0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva	N/A	N/A
Urine incontinence	Occasional (eg, with coughing, sneezing, etc); pads not indicated	Spontaneous; pads indicated	Interfering with activities of daily living; intervention indicated (eg, clamp, collagen injections)	Operative intervention indicated (eg, cystectomy or permanent urinary diversion)	N/A

[a]ADL: ability to perform activities of daily living.

[b]N/A: not applicable.

[c]BSA: body surface area.

[d]TPN: total parenteral nutrition.

[e]IV: intravenous.

Follow-up Assessments of Common PD Symptoms

A detailed follow-up of the different common manifestations of the disease and quality of life were examined at 3- and 6-month postinjection and then compared to baseline assessments. In addition, an over-the-phone subjective evaluation was performed 1 month after the first transplantation, in which a predesigned questionnaire was used to report any changes perceived by patients (Figure 3). The components of follow-up assessment are detailed in the following sections.

Figure 3. One-month posttransplantation subjective evaluation questionnaire.

Entity	Presence of subjective improvement (yes/no)
Change in type of medications	
Change in dose of medications/stopped medication	
Mood improvements	
Sleep disturbances and pattern	
Constipation	
Speech	
Balance	
Walking and ambulation	
Facial expression	
Upper extremity tremor	
Lower limb extremity	
Weight changes	
Appetite	
On/off periods	
Involuntary movements	

Disease Severity Assessments

Unified Parkinson Disease Rating Scale

The UPDRS serves as a disability and impairment scale for progression follow-up. It assesses changes in overall function and is divided into 4 sections: (1): evaluation of mentation, behavior, and mood (13-item assessment); (2) evaluation of activities of daily living, including speech, swallowing, handwriting, dressing, hygiene, falling, salivation, turning in bed, and wasting and cutting food (13-item assessment); (3) motor examination (18-item assessment of the right and left sides, and other body functions such as speech); and (4) motor complications (6-item assessment)

Unified Dyskinesia Rating Scale

The Unified Dyskinesia Rating Scale [15] evaluates involuntary movements or dyskinesia often associated with PD. There are 2 primary parts: (1) historical (part 1: on-dyskinesia; part 2: off-dystonia) and (2) objective (part 3: impairment; part 4: disability).

Motor and Functional Mobility Assessments

Mobility Lab

Mobility Lab [16] (APDM Inc) is a wearable mobility system that objectively assesses gait and balance, and has been validated for use in the PD population. It involves wearing wireless sensors on the wrists, ankles, and trunk. The participants wear the sensors while performing walking and turning tasks. Data are analyzed using the APDM software.

Nine-Hole Peg Test

The Nine-Hole Peg Test [17] is a specific test for finger and manual dexterity. Participants are asked to pick up 9 pegs one at a time from a container, using 1 hand only, and put them into holes as quickly as they can one at a time. They are required, without pausing, to remove the pegs one at a time and return them to the container as quickly as they can. Time taken to finish the task from the dominant and nondominant hands is used as the outcome measure.

Arabic Version of the Berg Balance Scale

The Berg Balance Scale (Arabic version) [18] is designed to objectively assess balance through 14 common functional activities that occur in everyday life. A higher score indicates a higher level of function.

Arabic Version of Activities-Specific Balance Confidence Scale

The Activities-Specific Balance Confidence Scale (Arabic version) [19] is a subjective measure of confidence in maintaining balance while performing various ambulatory and functional daily activities without falling or experiencing a sense of unsteadiness. A higher score indicates high confidence in maintaining balance.

Arabic Version of Falls Efficacy Scale-International

The Falls Efficacy Scale-International questionnaire (Arabic version) [20] is designed to assess the fear of falling in the older population and is recommended for use in people with PD. A higher score indicates that the person has a fear of falling. A lower score indicates high confidence in maintaining balance.

The Falls Efficacy Scale-International

For this assessment, each participant was asked to provide information about their history of falls at baseline, specifically at 1-month and 6-months pre-enrollment. In addition, information regarding the mechanism of falling was documented. Participants were contacted by research personnel every month postbaseline up to 6 months via phone to document falls.

Sensory Assessments

The University of Pennsylvania Smell Identification Test

The University of Pennsylvania Smell Identification Test [21] is commercially available for smell identification to test the function of an individual's olfactory system. It is the gold standard assessment of olfactory function among the smell identification tests for its high reliability (r=0.94) and practicality.

Arabic Version of the Pain Rating Scale

The Pain Rating Scale (Arabic version) [22] includes the visual analogue pain scale and assess different aspects of pain, including pain felt at the moment and pain felt in the past week. The Pain Rating Scale was translated by the British Pain Society and is recommended for use in populations for whom pain is a major issue.

Quality of Life and Psychological Well-being Assessments

Parkinson Disease Questionnaire

The Parkinson Disease Questionnaire [23] is a quality-of-life questionnaire designed to assess how often people with PD experience difficulties across 8 different criteria.

Arabic Version of Beck's Depression Inventory II

Beck's Depression Inventory II (Arabic version) [24] is a subjective measure of how depression manifests in behavior. It not only identifies varying levels of depression but is also able to indicate changes in depression and intensity of depression over a period of time. A high score indicates higher levels of depression.

Arabic Version of the Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (Arabic version) [25] is a self-reported measure that assess the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. A high score indicates higher levels of fatigue.

Cognitive Function Assessments

Montreal Cognitive Assessment

Montreal Cognitive Assessment [26] is a screening assessment tool for global cognitive function. It assesses several cognitive domains. A cutoff score of 25 is indicative of mild cognitive impairment.

Arabic Version of the Stroop Test

The Stroop Test (Arabic version) [27] is a measure of executive function that requires participants to inhibit the natural response (reading the letter X or a color word) and replace it with another response (the color of the letter X or the color of the word). Correct responses in 45 seconds are being used as the outcome measure.

The Symbol Digit Modalities Test

The Symbol Digit Modalities Test [28] is a measure of information-processing speed that requires participants to quickly say the number that matches a corresponding symbol. The total correct responses in 90 seconds are used as the outcome measure.

Sleep Quality Assessments

Arabic Version of the Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index (Arabic version) [29] is a well-validated and reliable measure of global sleep quality. It consists of 8 questions scored based on yes-or-no answers. If 3 or more items are answered yes, the person is at a high risk for obstructive sleep apnea.

Arabic Version of the Epworth Sleepiness Scale

The Epworth Sleepiness Scale (Arabic version) [30] is used to assess daytime sleepiness. It consists of 8 assessment items in which the participants use a 4-point Likert scale to rate how likely they would fall asleep in 8 different scenarios of daily activities. A score > 10 indicates the presence of daytime sleepiness.

Arabic Version of the STOP-Bang Questionnaire

The of the STOP-Bang Questionnaire (Arabic version) [31] is a simple and reliable diagnostic tool to screen participants at risk of obstructive sleep apnea. It consists of 8 questions scored based on yes-or-no answers. If 3 or more items are answered yes, the person is at a high risk for obstructive sleep apnea.

Arabic Version of the Insomnia Severity Index

The Insomnia Severity Index (Arabic version) [32] is a tool designed to assess the severity of both nighttime and daytime components of insomnia. It consists of 7 questions, and a score ≥10 is indicative of clinical insomnia.

Immune Modulation and Neural-Regeneration Biomarkers

A combination of indicators in the blood and cerebrospinal fluid are being examined to monitor treatment-related changes in the 2 treatment groups compared to baseline. This is necessary due to the lack of consensus on a single PD progression biomarker. For this, blood and cerebrospinal fluid samples at 3 time points were rapidly separated into single-use aliquots and frozen in –80 C^0 refrigerators at the same facility, thus ensuring sample quality is preserved until the end of the clinical trial. Two sets of multiplex enzyme-linked immunoassay kits were used on the Luminex 200 platform (Luminex Corporation) at CTC's proteomics laboratory according to the manufacturer's recommendations [33]. The first kit detects protein levels of α-synuclein and DJ-1/PD 7 (linked to neurodegeneration, as well as a proposed cognitive impairment marker, epidermal growth factor) [34,35]. Proinflammatory cytokines produced in the brain and peripheral blood are considered important cues in the disease. Therefore, the second kit will measure cytokine protein levels, including interleukin 1 beta, interleukin 6, interleukin 2, and tumor necrosis factor alpha [36,37].

In order to limit cross-batch variation, baseline, and 3- and 6-month posttreatment samples of each participant are being run on the same plate.

Statistical Analysis

For data analysis, SPSS 23.0 (IBM Corporation) will be used to perform all statistical analyses, with α=.05. A 2-sided, independent *t* test will be used to test the differences between the 2 study groups at baseline. Repeated measures analysis of variance will be used to test the effect of the intervention at different time points. Pearson correlation coefficient will be used to assess the relationship between the outcome measures of interest. Biomarker analysis will be performed using the Mann-Whitney statistical test.

Participant Withdrawal

According to the Helsinki declaration, participants have the right to withdraw from the study at any time and are informed of this right during the written informed consent process and during the study.

Data Management and Quality Control

The principal investigator, coinvestigators, research assistants, research coordinators, and medical doctors and nurses involved will ensure the good conduct of the data collection, data entry, and storage of relevant data.

All members of the research team will the protect the privacy of participants and the confidentiality of data. Personal identifiers have been limited on data collection forms, and all data files are being kept in a locked file cabinet. Data will be available only to appropriate members of the research team. Each participant has been given a unique identifier (symbol and number), and their electronic data are being stored in university network drives, with data collection occurring on an encrypted password-protected laptop computer.

To ensure quality control, blood samples will be analyzed in triplicate, and data entry will be cross-checked by a second person. All devices used for the biochemical testing and all subjective assessment tools included in this study have been validated. For biomarkers, samples are being measured in triplicate with the needed controls and standards included.

Results

The study protocol was approved by the institutional review board of the CTC on March 3, 2018. The study is being funded by the Deanship of Scientific Research at the University of Jordan. As of July 1, 2019, the date of the first patient accrual, 10 patients were enrolled in this study and thus participant recruitment has been completed. As of July 1, 2021, the status of the study is active and not recruiting. Study flow chart implementation, data collection, and data analysis are in

progress. The study is estimated to be completed in November 2021.

Discussion

PD is a neurodegenerative disease which imposes a socioeconomic burden on individuals and their relatives. Cellular therapy has proven its potential in several preclinical and clinical trials conducted in the past decades. A few studies have investigated the effect of MSCs on PD animal models and human participants. In one preclinical study, Jinfeng et al [38] showed that some PD symptoms were improved when umbilical cord–derived transduced MSCs were transplanted into a PD mice model. Stiffness of the limbs, unsteady gait, and uncoordinated limb movements were all alleviated after the stem cell treatment. Another study by Shetty et al [39] indicated that bone marrow–derived MSCs can be transdifferentiated adequately into functional dopaminergic neurons both in vitro and in vivo.

This protocol adopts a novel approach to PD cell–based therapy treatment. The novelty arises from 4 major points. The first is the choice and combination of stem cells. Umbilical cord–derived WJ-MSCs were chosen over other types of MSCs based on our earlier findings, which demonstrated an inherent advantage at the transcriptome level of this source of MSCs in terms of neurogenesis [40]. Cotransplanting allogenic NSCs in 1 arm is a unique aspect of the study, as the safety and effect of allogenic NSCs on PD symptoms have not been previously investigated. However, Harris et al [41] did pioneer the clinical use of human NSCs in a neuroinflammatory disease, with the long-term safety and tolerability of injecting autologous NSCs being reported in multiple sclerosis patients.

Second, the main goal of this phase I-II study is to examine the safety of using an allogenic source of MSCs for treatment which would remove individual variability in the MSC secretome observed when autologous stem cells are used as a source of cellular therapy [42]. Although similar clinical trials have sought to examine the safety of a treatment modality, there is scarcity and variability in the aspects assessed and reported by different groups. To improve reporting, our team compiled a tailored, comprehensive questionnaire with which the relevant TEAEs can be assessed according to a grade scale.

Third, the planned dual route of injection is consistent with published data regarding the benefits of intrathecal transplantations. Despite the invasiveness accompanying the procedure, delivering NSCs and MSCs via this route can decrease their chances of being trapped in the lungs and spleen [43]. The intravenous route was used simultaneously to account for the reported benefits and proposed mechanisms of action related to this route [44]. It is worth noting the study by Venkataramana et al [45] in which a single dose of bone marrow–derived MSCs was unilaterally transplanted into the sublateral ventricular zone by stereotaxic surgery into people with PD. Although their study did not report on the effectiveness of the treatment trialed due to the characteristics of the study (limited number of participants and being held in an uncontrolled manner), the results inspired subsequent studies—including our own—to consider cell-based therapy for PD.

Finally, this protocol includes extensive assessment tools for efficacy. Testing the feasibility of combining many measures that reflect the diversity of PD symptoms is of value to future trials regardless of the treatment under study. Although the 6-month follow-up period cannot assess the long-term effects of stem cell therapy, it is being used by many researchers to identify clinical changes in response to different treatment modalities [46].

Another aim of publishing this detailed protocol is to enable criticism and make room for improvement in the design of future trials. For instance, more tools for examining disease, such as neuroimaging and a larger panel of biomarkers, including microRNA, peptides, and metabolites can be added to future trials' assessment list [46]. Indeed, assessment tools used in this protocol have been carefully combined to cover many aspects of the disease. The APDM Mobility Lab system which is a validated, objective measure, captures gait impairments and postural instability which are amongst the most important motor complications influencing the functional quality of life in PD [47]. In addition, analyzing measured biomarkers during the course of therapy allows for a deeper insight into the changes related to the neurodegenerative and immune aspects of PD. This also provides a more personalized assessment of each participant to account for the lack of consensus on a specific progression marker in PD. Furthermore, the study design amply considers the nonmotor aspects of PD, which are often overlooked, as the burden of nonmotor symptoms, such as hyposmia, sleep disturbances, and cognitive impairments, significantly contribute to the overall poor quality of life among people with PD.

This detailed clinical trial protocol describes the many aspects related to the preparation and administration of stem cells, the recruitment of people with PD, and the safety and efficacy tools used to assess the therapy. It presents a model study design as it contains clear and direct procedures that may help neurologists and stem cell specialists engage in investigator-initiated clinical trials to assess the safety and value of this alternative therapeutic approach. Furthermore, sharing protocols with the scientific community encourages collaboration and the launching of multisite trials that improve participant numbers and result significance. Finally, due to the multifaceted nature of PD symptoms, interdisciplinary collaboration is key to achieving a medical breakthrough in this field.

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Authors' Contributions

FA and MA conceived the study and drafted the manuscript. AA gave final approval for the protocol and manuscript, SD contributed to the clinical aspects of the protocol, MWK contributed to the safety measure generation, and AAS contributed to the physical therapy measures.

Conflicts of Interest

None declared.

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Abbreviations

CTC: Cell Therapy Center
MSC: mesenchymal stem cell
NSC: neuronal stem cell
PD: Parkinson Disease
PBS: phosphate-buffered saline
TEAE: treatment-emergent adverse event
UPDRS: Unified Parkinson Disease Rating Scale
WJ-MSC: umbilical cord–derived mesenchymal stem cell

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Protocol

Modulation of Bone and Joint Biomarkers, Gut Microbiota, and Inflammation Status by Synbiotic Supplementation and Weight-Bearing Exercise: Human Study Protocol for a Randomized Controlled Trial

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Abstract

Background: There is strong evidence suggesting that prebiotics and probiotics regulate gut microbiota, reducing inflammation and thereby potentially improving bone health status. Similarly, mechanistic evidence suggests that either low-impact or high-impact weight-bearing exercises improve body composition and consequently increase bone mineral density in individuals with osteoporosis and osteoarthritis.

Objective: This study aims to investigate the effects of a synbiotic (probiotic+prebiotic) supplementation, an exercise intervention, or a combination of both on gut microbiota, inflammation, and bone biomarkers in postmenopausal women.

Methods: A total of 160 postmenopausal women from New Zealand will be recruited and randomized to one of four interventions or treatments for 12 weeks: control, synbiotic supplementation, exercise intervention, or synbiotic supplementation and exercise. The primary outcome measure is the bone and joint biomarkers at baseline and week 12, whereas the gut microbiota profile and inflammatory cytokine measurements will serve as the secondary outcome measures at baseline and week 12. Baseline data and exercise history will be used to assess, allocate, and stratify participants into treatment measures.

Results: Recruitment of participants will begin in September 2021, and the anticipated completion date is June 2022.

Conclusions: To the best of our knowledge, this will be the first randomized controlled trial to analyze the effects of both a synbiotic supplement and an exercise intervention in postmenopausal women. On the basis of the results obtained, a combination of synbiotic supplements and exercise might serve as a noninvasive approach to manage and/or improve body composition and bone health in postmenopausal women.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12620000998943p; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380336&isClinicalTrial=False

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KEYWORDS

synbiotic (prebiotic+probiotic); weight-bearing exercise; gut microbiota; inflammation; BMD; cytokines; bone and joint biomarkers

Introduction

Background

The global population is aging. The global incidence of postmenopausal osteoporosis is also increasing [1,2]. Postmenopausal osteoporosis is characterized by increased low-grade inflammation that contributes to low bone mass and degradation of bone mineral content, resulting in postmenopausal bone loss [3-5]. Elevated levels of proinflammatory cytokines (eg, interleukin [IL]–6, tumor necrosis factor [TNF]-α, IL-1, and receptor activator of nuclear factor kappa-B ligand produced by activated T cells) induce osteoclast formation and activity during senescence [2,6]. Meanwhile, it is well recognized that conventional estrogen therapy in the form of hormone replacement therapy (HRT), such as estradiol implants, increases bone density by increasing the activity of osteoblasts, reducing bone resorption, and reducing inflammation [7-9]. However, the long-term use of HRT as an anabolic treatment and high doses of estrogen may not reduce the incidence of bone fracture [7] and are associated with long-term side effects. Therefore, nutritional interventions are safe and reliable for improving bone health status.

Studies have reported that changes in the gut microbiome can affect distant organs, including the bone and subsequently the development of osteoporosis [10]. Recent studies in rats and mice have suggested that the gut microbiome modulates immune status [11] as well as calcium absorption and molecular control of bone resorption [12-14]. Although studies have been conducted in animals, there are few studies in humans that have investigated the effects of pre- and probiotics on the gut microbiome and postmenopausal osteoporosis. Moreover, human gut microbiota is different from that of rodents, which is why many studies have faced limited success in their attempt to *humanize* the murine microbiota [15].

Defining Osteoporosis and Its Significance

Osteoporosis is “characterized by low bone mass and microarchitectural deterioration of bone tissues, consequently increasing bone fragility and breakage” [16]. The term osteoporosis (*osteoun*) refers to *bone* and *pór* (*os*) to *passage+osis* [17]. The widely accepted clinical diagnostic criteria and intervention threshold are defined as bone mineral density (BMD) ≥2.5 SDs (T score ≤−2.5) below the mean value of a young reference at the lumbar spine, femur neck, or total hip bone in older men and postmenopausal women [18].

The vast burden of osteoporosis constitutes an increase in morbidity and mortality [19], loss of quality-adjusted life-years (QALYs) [20], and a continuous rise in the cost of health care services, such as clinics, nursing homes, and hospitals [21,22]. It is a growing global health concern, with the lifetime risk of sustaining any fracture at approximately 50% for women and 20% for men in individuals aged >50 years living in Western countries [23]. It has also been predicted to become an issue in developing countries as the aging population rises. The risk of fracture becomes higher as people age, especially in postmenopausal women [24].

In 2011, osteoporosis-related QALYs were found to be 11,249, with a projection of 13,205 and 15,176 for 2013 and 2020, respectively, because of fractures. The results also suggest that there are more QALYs for women (6028) than men (5221) [22].

As a global epidemic situation, the International Osteoporosis Foundation suggests that 33% of middle-aged women and 20% of men (aged >50 years) will have an osteoporotic fracture [25]. The disease constitutes an economic burden, particularly because of the high cost of treatment. Over US $300 million per annum is estimated to be spent on treating fractures, whereas the total cost is estimated at US $1.15 billion per annum in health costs, posing a heavy burden on health care service providers in New Zealand [20].

Physical Activity

Physical activity is defined by the World Health Organization as any “bodily movement of the skeletal muscle, which requires energy expenditure” [26]. Physical activity enhances the composition and function of the human skeletal system. However, skeletal muscle performance also deteriorates with age [27], and a lack of exercise and physical activity has been linked to bone loss and ultimately osteoporosis [28]. Osteoporosis may cause falls that result in osteoporotic fractures in older women.

Previous studies, including Cochrane reviews, have reported the effects of physical activity on bone strength across the life spans [29] of children and adolescents [30] as well as women, especially postmenopausal women [31-33]. A study from Italy reported progressive resistance strength training of the lower limbs to be most effective for the neck of the femur BMD in patients with osteoporosis. In contrast, a multicomponent training program was suggested for a spine BMD intervention [34].

Neilson et al [35] have defined activity energy expenditure (AEE) as “a modifiable component of total energy expenditure (TEE) derived from both volitional and non-volitional activities.“ Total energy expenditure comprises multiple components, including physical activity energy expenditure, resting energy expenditure, and the thermic effect of food [36]. The impact of physical activity has been used to alleviate several obesity-related diseases and the overall burden of diseases in men and women alike [37].

The Research

Overview

The gut microbiome could be a plausible target for the modulation of bone disorders in the aged, as it has been associated with the innate and adaptive immune system. Our previous study inquired into the association between the gut microbiome and bone health status based on the World Health Organization classification of osteoporosis among postmenopausal women [38]. The relationship between the composition and predictive function of gut microbiota in women and their bone density, classified into healthy and osteopenic or osteoporotic groups, was investigated. The findings of this recent study showed that α diversity of the microbial profiles differed based on the hip and femoral neck osteoporosis

classifications. Meanwhile, β diversity principal component analysis by using the Bray-Curtis index showed differences based on femoral neck classifications. Positive correlations were observed between *Lactobacillus*, *Bacillus*, *Paenibacillus*, and *Geobacillus* (all from the phylum Firmicutes) and BMD at all sites. However, negative correlations were reported for *Bacteroides* and *Parabacteroides* and all BMD sites [39,40]. This finding agrees with previous reports that showed the importance of the *Lactobacillus* species in bone maintenance [14,41]. This result was similar to that of Li et al [42], who showed a negative correlation between *Bacteroides* and BMD.

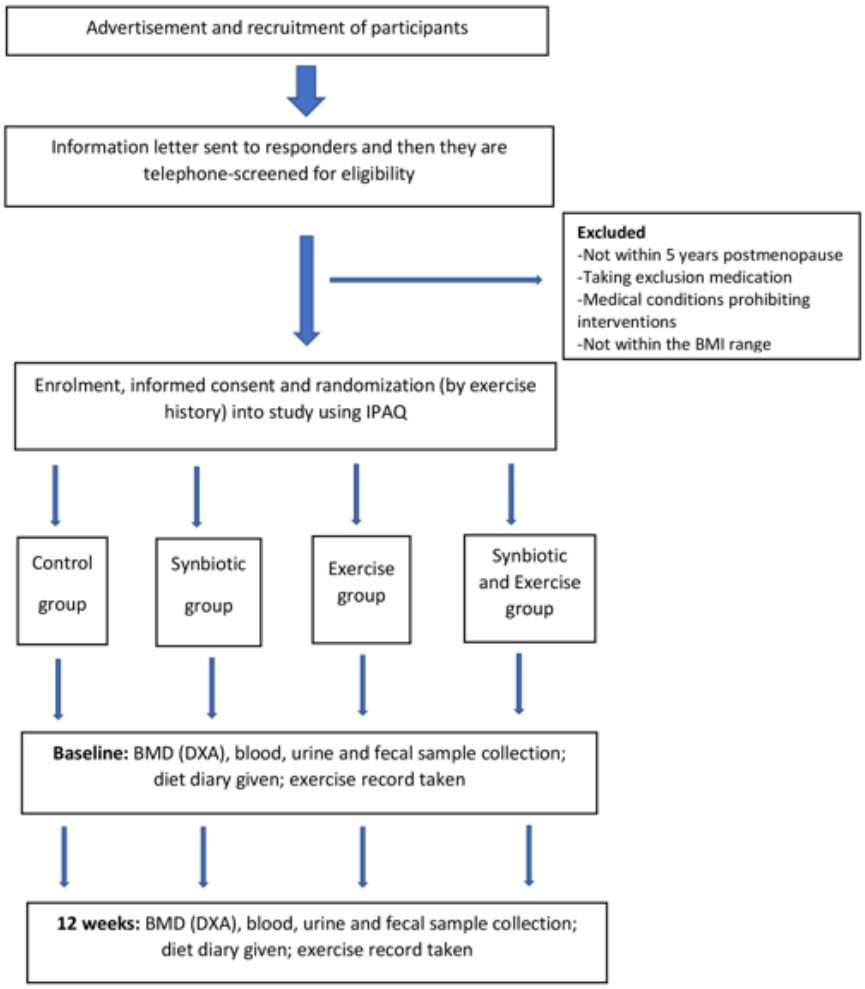
In addition, a study conducted with ovariectomized rats showed the effects of probiotics, prebiotics, and synbiotics on mineral (calcium and phosphorus) metabolism and absorption. The effects were also observed in the form of higher *Bifidobacteria* and *Bacteroides* counts, lower pH, and reduced bone turnover. The intervention also resulted in a tendency toward lower bone alkaline phosphatase [43].

Therefore, modulation with a synbiotic food supplement and weight-bearing low-impact exercise (interventions) can be used to provide data that may contribute to improvements in osteoporotic patient care. This study will use a prospective stratified (by exercise history), randomized, 4-group experimental design with 2 major data collection points (baseline and week 12). Before randomization, participants will be stratified by exercise history (≥2 high-intensity exercise sessions per week and <2 sessions per week) using the International Physical Activity Questionnaire to ensure equal distribution among the 4 groups. However, all participants would be permitted to continue their usual physical activity regime.

Research Questions

What are the effects of dietary interventions with synbiotic food supplements and weight-bearing exercises on bone metabolism, gut microbiota, and micronutrient or inflammation status in postmenopausal women? Do specific gut microbiota alterations moderate bone metabolism? How do individual differences in nutritional interventions affect gut microbiota and, subsequently, bone metabolism? Ultimately, can they be used as a treatment for postmenopausal osteoporosis? Our principal hypothesis is that improvement in bone health, gut microbiota, and inflammation status will be greater in participants randomized to the synbiotic+exercise group compared with participants in the control, synbiotic, or the exercise groups (Figure 1).

Figure 1. Cartilage oligomeric matrix protein 4 Bones clinical study flowchart. BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; IPAQ: International Physical Activity Questionnaire.



Specific Aim

This study aims to examine whether supplementation of fermented milk or dairy (yogurt) with a synbiotic (probiotic+prebiotic) and weight-bearing low-impact exercise could be effective in achieving favorable changes in gut microbiota, inflammation status, and biochemical indexes of bone and joint metabolism.

Aim 1: to compare control, synbiotic, exercise, and synbiotic+exercise groups based on changes in the gut microbiota using 16S rDNA sequencing at baseline and week 12.

Aim 2: to compare control, synbiotic, exercise, and synbiotic+exercise groups based on changes in inflammation status (inflammatory cytokines) at baseline and week 12.

Aim 3: to compare control, synbiotic, exercise, and synbiotic+exercise groups based on changes in bone formation (procollagen type 1 N-terminal propeptide [P1NP]), resorption (cross-linked C-telopeptide of type 1 collagen [CTx-I]), and joint degradation (CTx-II/COMP [cartilage oligomeric matrix protein]) at baseline and week 12.

Aim 4: to compare control, synbiotic, exercise, and synbiotic+exercise groups based on changes in body composition (lean body mass and fat mass), total hip, femoral neck, and spine BMD (DXA [dual-energy x-ray absorptiometry]) at baseline and week 12.

Methods

Participants

The G*Power statistical software, version 3.1.9.7, developed in Heinrich Heine University Düsseldorf, was used to calculate the sample size using the bone biomarker CTx-I; a recommended number of 36 women would be required for the study. However, 40 women aged >60 years will be recruited for each of the 4 groups to allow for a possible dropout rate of 10%. The test groups will receive the synbiotic food supplementation and exercise program (10,000 steps brisk walking per day required), whereas the control group will receive a placebo and no exercise; however, dietary intake and exercise will be monitored by a 3-day diet diary and the International Physical Activity Questionnaire. All study participants will read the information sheet, and signed and written consent forms will be obtained from them.

Inclusion Criteria

The inclusion criteria include a confirmed menopause diagnosis (by an initial blood test—baseline screening—that includes checking the levels of follicle-stimulating hormone [≥30 mIU/mL] and estrogen) of at least five years based on no menstruation and the BMI of all participants will be between 17 and 35 kg/m².

Exclusion Criteria

The following criteria are to be confirmed by medical history or measurements:

1. Use of HRT
2. Biphosphonates in the past 6 months
3. Currently on estrogen, tamoxifen, aromatase inhibitors, or other antiresorptive or anabolic treatments of osteoporosis
4. A liver function test or creatinine level above the normal range, or any other history suggesting liver or kidney disease to be confirmed by baseline screening
5. Incidence of diabetes mellitus by using the questionnaire and baseline screening
6. Participants with an estimated BMD T score <−2.5 or fragility fracture in the previous 6 months
7. Antibiotic intake in the previous 6 months
8. Smoking and intake of alcohol >2 units per day

The following criteria are to be confirmed by the baseline questionnaire:

1. Participants' intake ability and allergic reactions to probiotic and prebiotic supplements
2. Intake of multivitamins and mineral supplements (prescribed or over the counter), antibiotics, or use of any other medication known to affect bone metabolism and/or gut microbiota
3. Presence of any systemic disease
4. Use of any medications such as HRT, glucocorticoids, estrogen, systemic cortisone, bisphosphonates, diuretics, antibiotics (for the gut microbiota), or other steroid hormones
5. Active physical activity, that is, ≥60 minutes of vigorous or moderate activity for ≥3 days.

The Intervention: COPES-4-Bones Clinical Study

The study design is a randomized controlled trial (RCT). All the volunteer participants in the trial will undergo the following.

Health Questionnaire and Health Screening

Blood Test for the Initial Baseline Screening

Fasting blood samples will be collected at baseline for (bone biomarkers and inflammatory cytokines) routine laboratory tests as well as medical examinations to ensure that the participants are in good health. Abnormal results from this trial will be recommended for discussion with their doctors.

Initial Anthropometry at Baseline

The body weight of participants will be measured using a weight scale to the nearest 0.1 kg, and standing height will be measured using a stadiometer to the nearest 0.1 cm wearing light clothes and no shoes. BMI will be calculated as weight divided by height squared (kg/m²). Waist to hip ratio will be determined by measuring the waist and hip circumference to the nearest 0.1 cm using a nonstretchable tape. Other body composition measurements will be analyzed with DXA.

Baseline Questionnaire

The baseline questionnaire will include the following: sociodemographic, activity index and level, medications taken in the last 6 months, smoking status, and alcohol intake.

For Inclusion

Diet or Food Records

The dietary assessment of the intake of fermented milk and dairy products, including total energy, protein, minerals, and vitamin D, will be based on a 3-day diet diary. Face-to-face interviews by the principal investigator will ascertain the food record.

Venous Fasting

Blood, fecal, and urine samples will be collected at baseline and week 12. Blood will be collected by a phlebotomist between 8 and 10 AM after 12 hours of fasting (overnight). Table 1 shows all the variables that will be measured, rationale, and the methods to be used.

1. Fasting blood samples: blood samples will be collected at baseline and week 12, the end of the study, for the following:
    - Bone metabolism markers: concentrations of serum or plasma total osteocalcin, CTx-I, total P1NP, and 25-hydroxyvitamin D will be measured using immunoassay kits and Roche Elecsys.
    - Cartilage degradation markers: COMP precursor and CTx-II from serum will be measured.
    - Parathyroid hormone and lipid profile tests will be measured using immunoassay kits.
    - Inflammation markers: concentrations of inflammatory cytokines by BioLegend LEGENDplex Multi-Analyte and hs-CRP (high-sensitivity C-reactive protein) will be measured.
2. Spot urine samples: samples of a midstream urine specimen voided spontaneously by the participants will be collected at baseline and at the end of the study and tested for protein, creatinine, and electrolyte content as well as CTx-II by ELISA (enzyme-linked immunosorbent assay).
3. Fecal samples: samples will be collected at baseline and at the end of the study (week 12). The total genomic DNA will be extracted, and 16s ribosomal DNA will be amplified, prepped, and sequenced.

Table 1. Study outcome measures and rationale for use.

Variables	Rationale	Methods	Baseline	Week 12
Blood analyses				
OC[a]	Bone formation markers	Electrochemiluminescence immunoassay using the Roche COBAS e411 system (Roche Diagnostics)	✓[b]	✓
P1NP[c]	Bone formation markers	Electrochemiluminescence immunoassay using the Roche COBAS e411 system (Roche Diagnostics)	✓	✓
CTx[d]-I	Bone resorption marker	ELISA[e]	✓	✓
25(OH)D[f]	Serum Vit D to determine the amount of circulating vitamin	Isotope-dilution liquid chromatography-tandem mass spectrometry	✓	✓
COMP[g]	Cartilage degradation markers	ELISA	✓	✓
CTx-II	Cartilage degradation markers	ELISA	✓	✓
PTH[h]	To assess the regulation of serum calcium concentration	Electrochemiluminescence immunoassay using the Roche COBAS e411 system (Roche Diagnostics)	✓	✓
Lipid profile	To assess the lipid profile	Electrochemiluminescence immunoassay using the Roche COBAS e411 system (Roche Diagnostics)	✓	✓
Inflammatory cytokines	To assess the inflammatory status	BioLegend LEGENDplex Multi-Analyte	✓	✓
hs-CRP[i]	To assess the inflammatory status	Electrochemiluminescence immunoassay	✓	✓
Gut microbiota data	To determine changes in the bacterial community	16s ribosomal DNA	✓	✓
Diet diary	To obtain dietary intake data	3-day diet diary	✓	✓
Exercise history record (IPAQ[j])	For initial randomization	IPAQ	✓	✓
Baseline questionnaire (sociodemographic and medication history record)	To obtain sociodemographic status and history	Questionnaires	✓	✓
Wearable fitness tracker record	To obtain exercise regime data	Wearable fitness tracker	✓	✓
Adherence to synbiotic supplement and exercise	Documentation of unused supplements or prescribed exercise session attendance	Record keeping	✓	✓
Anthropometry	Weight, height, and waist circumference measured by a researcher at Massey University	Tanita electronic scale and stadiometer	✓	✓
DXA[k]	BMD at the total hip, femoral, neck and spine (L1-L4) and body composition	DXA using Hologic QDR series Discovery A, Bone densitometer, and Apex system software version 4.5.3	✓	✓

[a]OC: osteocalcin.

[b]Variable accessed.

[c]P1NP: procollagen type 1 N-terminal propeptide.

[d]CTx: cross-linked C-telopeptide.

[e]ELISA: enzyme-linked immunosorbent assay.

[f]25(OH)D: 25-hydroxyvitamin D.

[g]COMP: cartilage oligomeric matrix protein.

[h]PTH: parathyroid hormone.

[i]hs-CRP: high-sensitivity C-reactive protein.

[j]IPAQ: International Physical Activity Questionnaire.

[k]DXA: dual-energy x-ray absorptiometry.

DXA Measurements

Body composition, bone mineral content, BMD, and T scores of the femoral neck, lumbar spine, and hip will be measured in participants at baseline screening.

All exercise intervention and synbiotic+exercise groups or participants will be given a wearable fitness tracker to wear during the exercise (brisk walking) of 10,000 steps. The Borg Rating of Perceived Exertion will be used to calculate intensity. Table 2 shows the interventions and dosage per participant.

Table 2. Intervention and dose administered to participants in each group.

Intervention and treatment groups	Description	Daily intake per day
Synbiotic	• Probiotic supplement • Prebiotic supplement	• 10 billion colony forming units of *Lactobacillus sp.* • 8 grams of prebiotic fiber (inulin)
Exercise	• Weight-bearing exercise	• 10,000 steps
Placebo	• Placebo	• Placebo with maltodextrin

Statistical Analyses

G*Power statistical software version 3.1.9.7 developed in Heinrich Heine University Düsseldorf was used to calculate the sample size to ensure 95% CI with an α value of .05. We require 36 participants for each group. The within-subject SD for the primary outcome variables CTx-I and P1NP with a correlation of 0.5 was used. The number of volunteers was increased to 40 to allow for a dropout rate of 10%.

The results will be presented as either percentages or mean differences. Normality tests will be assessed through Shapiro-Wilk tests carried out on each parameter before analysis. The conventional analysis of variance (ANOVA) for RCT analysis will be used, and ANOVA for repeated measures will be applied to study treatment differences, period effect, and the interaction between treatment and period (carryover effect). IBM SPSS version 25 and Minitab statistical software version 19 (Minitab LLC) will be used for statistical analyses. Comparing groups' pretest with Mann–Whitney U test and then comparing pre- and postintervention results with Wilcoxon is one option and transforming data into ranks and performing an analysis of covariance (or ANOVA) is another option. All analyses will be considered statistically significant at $P \leq .05$.

Results

Ethics and Collection of Data

Ethical approval for this study has been received from the Health and Disability Ethics Committee of New Zealand. The recruitment and collection of data will begin in September 2021. We aim to complete data collection by June 2022. Statistical analyses, report writing, and dissemination of results are expected to be completed by February 2023. Funding is being sought for the study.

Expected Benefits or Outcomes

The anticipated outcomes of this study are a reduction in bone turnover as measured using CTx-I as a marker, as well as a reduction in inflammation (reduced or changed levels of specific cytokines such as hs-CRP, IL-6, and TNF-α).

With menopause and the loss of estrogen, bone turnover (formation and resorption) increases significantly. Over time, because of increased levels of IL-6 and inflammation, bone resorption (breakdown) overtakes bone formation, and this increase in bone resorption can be measured using the marker CTx-I. Several studies over the past 20 years have shown that a reduction in CTx-I is associated with long-term changes in bone density and a reduction in fractures. CTx-I most sensitively reflects the change in bone resorption after mineral supplementation or increased absorption of calcium and can predict the rate of bone loss and fracture risk in postmenopausal women. CTx-I may reflect parameters of bone strength unrelated to BMD, such as microarchitectural deterioration of bone tissue resulting in microcracks that act as stress risers or trabecular perforation.

Supplementation with a synbiotic will modify the gut microbiota and improve calcium and magnesium absorption. Prebiotic supplementation promotes bacterial growth that induces nondigestible carbohydrate fermentation, increases short-chain fatty acids (SCFAs), and reduces the pH of the gut, thereby increasing calcium absorption. The reduction in pH promotes the growth of bacteria that are less likely to cause inflammation, and SCFAs stimulate the effects of anti-inflammatory cytokines. Probiotic supplementation by *Lactobacillus* and *Bacillus* species may promote an immunoprotective response in the gut mucosa by reducing the levels of systemic inflammatory cytokines and preventing the reduction in bone density.

Discussion

Principal Findings

Degeneration of bone health in the form of osteoporosis, osteoporotic fractures, and osteoarthritis are major health care issues leading to a significant increase in morbidity and mortality in New Zealand and all over the world. Similarly, the growing number of patients with osteoporosis or osteoarthritis results in huge health care costs. The aim is to measure the effect of synbiotics, weight-bearing exercises (10,000 brisk walking steps per day), or a combination of both on gut microbiota, inflammation status, and bone health. This study is important for several reasons. This study is directed toward postmenopausal women who have experienced a rapid phase of bone loss 5 years postmenopause. The use of a synbiotic (a combination of probiotic and prebiotic) supplement is particularly novel in the modulation of the immune system, gut microbiota, and anti-inflammatory response. Studies are needed

to measure the effects of synbiotic supplementation and weight-bearing exercise on gut microbiota, inflammatory status, and bone health. Randomization by exercise history will help eliminate the effects of the previous exercise regime for the study. There is a critical need for measures of bone turnover and not BMD only as a primary outcome.

The effects of probiotic or synbiotic supplementation on markers of inflammation have also been reported. A reduction in proinflammatory cytokines (eg, IL-1β, TNF-α, IL-6, and IL-8) and an increase in anti-inflammatory cytokines (IL-10 and IL-4) [44] were observed in response to these interventions. Similarly, studies have indicated the protective factors of probiotic supplementation [45] and exercise in bone metabolism and health [34]. Long-term participation in a relevant and targeted exercise regime is known to improve bone mechanical properties over time [46].

Synbiotics: Mechanism of Action

Prebiotic supplementation promotes bacterial growth that induces nondigestible carbohydrate fermentation, increases SCFAs, and reduces the pH of the gut contents, thereby increasing calcium absorption. The reduction in pH promotes the growth of bacteria that are less likely to cause inflammation, and SCFAs stimulate the effects of anti-inflammatory cytokines. In addition, probiotic supplementation with *Lactobacillus* and *Bacillus* species promotes immunoprotective response or effects in the gut, reducing inflammatory cytokines and preventing the reduction in bone density [47].

Markers of Bone Turnover

Prediction of bone loss and risk of fractures is conducted using biomarkers of bone turnover independent of bone density in women. The occurrence of menopause results in a period of bone loss, where the rate of bone resorption exceeds that of formation (approximately 5 years). A bone remodeling cycle of formation and resorption takes place between 4 and 6 months, replenishing approximately 5%-15% of the total bone mass in a year [46]. These data provide the rationale for the length of time and a comprehensive investigation of body composition and bone turnover status in the study described here.

The strength of the RCT will account for exercise history and the sample size and duration to ensure an adequately powered sample needed to detect clinically and statistically significant results.

Ethics and Dissemination

Ethics

The study received ethical approval from the Health and Disability Ethics Committee of New Zealand.

Safety and Data Monitoring

The principal investigator and team will monitor the conduct, safety, and scientific integrity of the proposed clinical trial. Routine laboratory measurements, including liver and kidney function tests, blood glucose (nonfasting), and lipid profile (triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) tests, will be performed at baseline and 12 weeks. Individuals with results that are outside the clinical range will be contacted and referred to their general practitioner. The safety precaution will be to inform all participants to report any effects of treatment, and in the unlikely event that 20% of the participants report severe diarrhea, a discontinuation of the study will be triggered. Each report will include the monitoring of compliance with informed consent and eligibility requirements, compliance with the recruitment plan according to protocol, follow-up data collection according to the protocol, expected and actual accrual, protocol violations, and patient withdrawals from the study.

Dissemination

A lay summary of the report will be communicated to all study participants. The results of the study will also be disseminated at various seminar presentations and feedback sessions at the College of Health, School of Health Sciences, Massey University, Palmerston North, New Zealand, and in manuscripts that will be submitted to a peer-reviewed journal.

Strengths and Limitations of This Study

This study was designed as an RCT to account for exercise history, and the sample size and duration have been selected to ensure an adequately powered sample needed to detect clinically and statistically significant results. In this study, investigating the effects of both prebiotics and probiotics with and without weight-bearing exercise provides strong evidence for an RCT. The limitation of the study lies in the inability to extend the duration in terms of further follow-up.

Conclusions

Our research study aims to decrease the possibility of osteoporotic fractures resulting because of the incidence of inflammation and loss of bone mass by improving body composition (lean and fat mass) among postmenopausal women after ≥5 years. This study compares the effectiveness of synbiotic supplementation and weight-bearing exercise intervention, both of which may be used as a therapy for bone health maintenance in postmenopausal women. To the best of our knowledge, this will be the first RCT to analyze the effects of both a synbiotic supplement and an exercise intervention in postmenopausal women. On the basis of the results obtained, a combination of synbiotic supplementation and exercise might serve as a noninvasive approach to manage and/or improve body composition and bone health in postmenopausal women.

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Authors' Contributions

MCK, NCR, and BLI conceptualized the research and reviewed the manuscript. BLI wrote the first draft. All authors contributed, reviewed, and approved the submitted version.

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
BMD: bone mineral density
COMP: cartilage oligomeric matrix protein
CTx-I: cross-linked C-telopeptide of type 1 collagen
DXA: dual-energy x-ray absorptiometry
ELISA: enzyme-linked immunosorbent assay
HRT: hormone replacement therapy
hs-CRP: high-sensitivity C-reactive protein
IL: interleukin
P1NP: procollagen type 1 N-terminal propeptide
QALY: quality-adjusted life-year
RCT: randomized controlled trial
SCFA: short-chain fatty acid
TNF: tumor necrosis factor

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Protocol

mHealth Messaging to Motivate Quitline Use and Quitting: Protocol for a Community-Based Randomized Controlled Trial in Rural Vietnam

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Abstract

Background: Tobacco kills more than 8 million people each year, mostly in low- and middle-income countries. In Vietnam, 1 in every 2 male adults smokes tobacco. Vietnam has set up telephone Quitline counseling that is available to all smokers, but it is underused. We previously developed an automated and effective motivational text messaging system to support smoking cessation among US smokers.

Objective: The aim of this study is to adapt the aforementioned system for rural Vietnamese smokers to promote cessation of tobacco use, both directly and by increasing the use of telephone Quitline counseling services and nicotine replacement therapy. Moreover, we seek to enhance research and health service capacity in Vietnam.

Methods: We are testing the effectiveness of our culturally adapted motivational text messaging system by using a community-based randomized controlled trial design (N=600). Participants were randomly allocated to the intervention (regular motivational and assessment text messages) or control condition (assessment text messages only) for a period of 6 months. Trial recruitment took place in four communes in the Hung Yen province in the Red River Delta region of Vietnam. Recruitment events were advertised to the local community, facilitated by community health workers, and occurred in the commune health center. We are assessing the impact of the texting system on 6-month self-reported and biochemically verified smoking cessation, as well as smoking self-efficacy, uptake of the Quitline, and use of nicotine replacement therapy. In addition to conducting the trial, the research team also provided ongoing training and consultation with the Quitline during the study period.

Results: Site preparation, staff training, intervention adaptation, participant recruitment, and baseline data collection were completed. The study was funded in August 2017; it was reviewed and approved by the University of Massachusetts Medical School Institutional Review Board in 2017. Recruitment began in November 2018. A total of 750 participants were recruited from four communes, and 700 (93.3%) participants completed follow-up by March 2021. An analysis of the trial results is in progress; results are expected to be published in late 2022.

Conclusions: This study examines the effectiveness of mobile health interventions for smoking in rural areas in low- and middle-income countries, which can be implemented nationwide if proven effective. In addition, it also facilitates significant

collaboration and capacity building among a variety of international partners, including researchers, policy makers, Quitline counselors, and community health workers.

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International Registered Report Identifier (IRRID): DERR1-10.2196/30947

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KEYWORDS

tobacco cessation; smoking cessation; mHealth; global health; Vietnam; randomized controlled trial

Introduction

Background

Tobacco is a leading preventable cause of mortality, killing more than eight million people each year, mostly in low- and middle-income countries [1]. Although effective smoking cessation aids are available [2], the use of pharmacological cessation aids combined with behavioral counseling doubles the chances of successfully achieving long-term cessation [3]. Unfortunately, these treatments are often underutilized, especially in low- and middle-income countries, where the rates of tobacco use are high. In Vietnam, 44% of men and 1% of women smoke [4]. Evidence-based interventions are underused in Vietnam: only 24% of smokers have used nicotine replacement therapy (NRT), patch, or chewing gum; less than 1% have used prescription medication to try and stop smoking; and only 3% of smokers attempting to quit in Vietnam report receiving counseling [5]. Most smokers in rural Vietnam are thinking of quitting but are not ready to quit the next month [5]. In 2015, the Vietnam Ministry of Health established two telephone *Quitlines*, based in northern Vietnam (the Bach Mai Hospital's Quitline) and southern Vietnam (the Binh Dan Hospital's Quitline) to engage and motivate Vietnamese individuals to quit smoking cigarettes. However, these services are underused, and interventions are needed to improve the uptake of these Quitlines and improve the quitting rate in Vietnam.

Objectives

The objectives of this study are as follows:

- To adapt an existing cessation texting system that has proven effective in the United States [6] to the Vietnamese context, encouraging smokers in rural settings of northern Vietnam to accept counseling services from the existing Bach Mai Hospital Quitline and motivating smokers to quit.
- To conduct a randomized controlled trial to test the effectiveness of the adapted motivational text messaging intervention in improving smoking cessation in a sample of 600 rural Vietnamese smokers.
- To implement capacity building activities for staff at the Bach Mai Quitline.

We hypothesize that participants in the intervention arm will have higher rates of cessation and higher smoking self-efficacy and that they will engage more frequently with the Quitline counseling and NRT services.

Methods

Intervention Development and Adaptation

Intervention Overview

In this study, participants are randomized to receive either (1) motivation and assessment text messages that encouraged smoking cessation via Quitline service and NRT engagement (intervention group) or (2) assessment text messages only (comparison group). The text message system is intended to encourage the uptake of cessation services and is, hence, an augmentation of, not a replacement for, regular appropriate clinical services.

Message Content and Sequencing

Our message database from a prior study in the United States included both expert and peer-written messages. The expert-written motivational messages were iteratively developed through a group review, with content guided by current guidelines and social cognitive theory [7]. The peer messages were advice messages written by smokers to other smokers. The combination of these messages increased smoking cessation rates in our prior US study. Expert-written messages provided important theory- and guideline-based health information to the participants. The peer messages touched on more social aspects (dealing with family and cost) than expert messages and increased longitudinal engagement of the intervention compared with the expert messages [7].

We used a two-step process to develop a similar database for this study in the Vietnamese language. First, we adapted the expert-written motivational messages that were previously developed in English iteratively through a group review, with content guided by current guidelines and social cognitive theory. After the messages were professionally translated to Vietnamese, consultants (former smokers who had used the Bach Mai Quitline services) and professionals reviewed the existing messages and were asked to identify messages that they liked and disliked. Deriving culturally appropriate message content using peer messages was especially important in this study because it was the first time that the intervention had been implemented in Vietnam. Therefore, 10 consultants (former smokers who had used the Quitline in Vietnam) were invited to draft new text messages based on prompts such as "I called the Bach Mai Quitline when..." and "I quit smoking because..." The research team then eliminated messages that were incomplete, unclear, or clearly redundant and established a set of shortlisted messages. This process is outlined in the *Results* section.

In addition to these one-way motivational text messages, the research team developed a series of two-way assessment messages in Vietnamese. All participants (intervention and control arms) received the following text message every two weeks: “How many times have you smoked tobacco in the past 24 hours?” while intervention participants also received a Quitline-related question every other week: “Would you like a call from a Bach Mai Quitline smoking counselor?” If they replied with a “yes,” the Quitline would call them back. The final sequences of the messages were collaboratively reviewed and approved by the research team.

Bach Mai Quitline

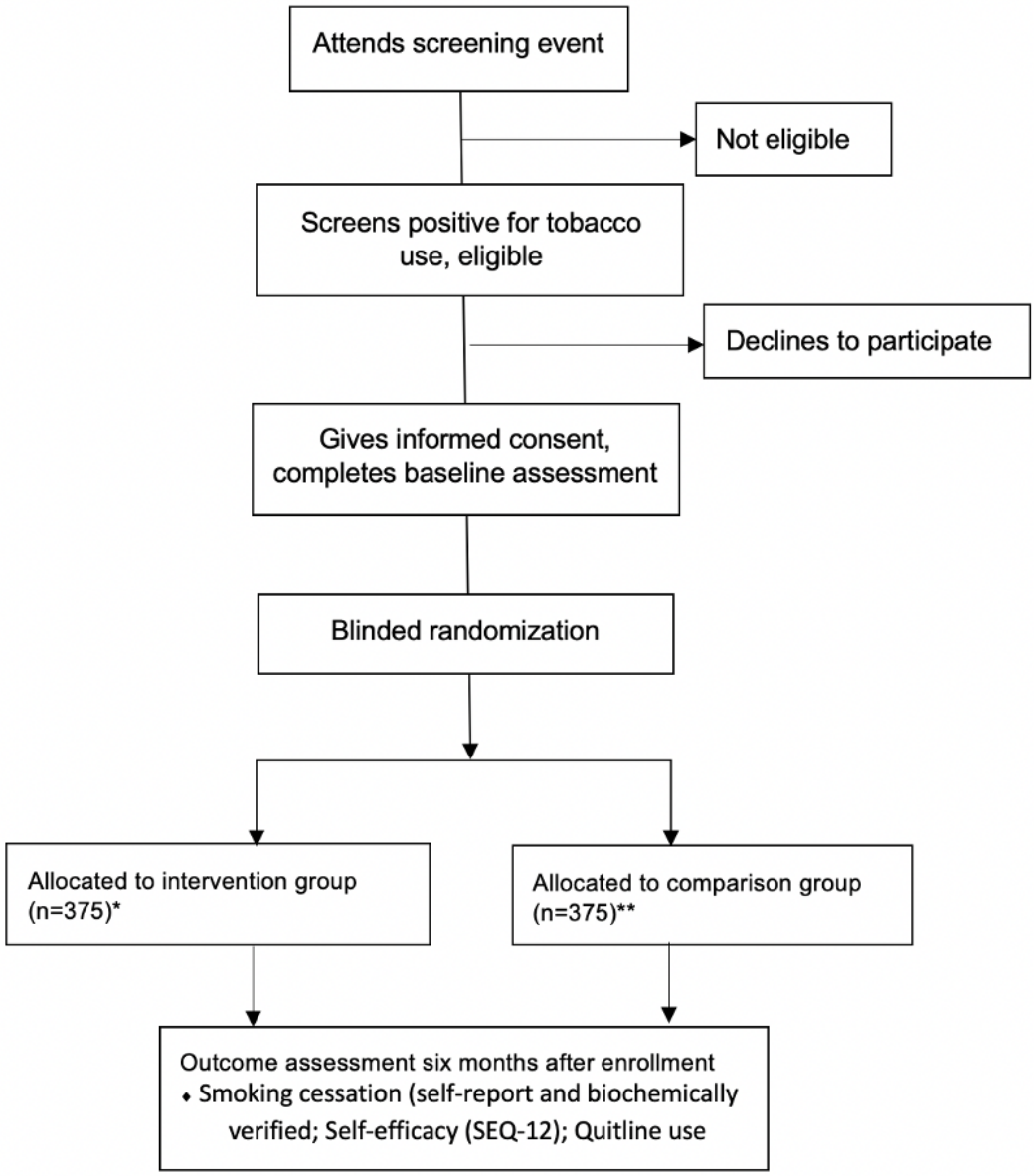
Quitlines have been demonstrated to be an effective intervention for smoking cessation [8]. Trained counselors can help callers select the appropriate cessation services for them and can offer call-back strategies to maximize adherence to NRT and help with relapse prevention. Interventions to increase the use of Quitlines have included connecting with clinics and email and text motivational reminders [9]. The Bach Mai Quitline in Vietnam is staffed by certified tobacco treatment specialists (registered nurses and public health professionals) who have been trained in principles of motivational interviewing, evidence of the risks associated with tobacco, benefits of phone-based counseling, and strategies summarized in the 2008 US Treating Tobacco Use and Dependence guidelines [10] including the *5As* (Ask, Advise, Assess, Assist, and Arrange) and the *5Rs* (Relevance, Risks, Rewards, Roadblocks, and Repetition). In this study, the team at the University of Massachusetts Medical School (UMMS) conducted site visits and additional training for the Bach Mai Quitline staff. This additional training totaled 10 hours, used a combination of didactics and role plays, and covered topics such as pharmacotherapy, behavioral interventions for smoking cessation, motivational interviewing, individual counseling, telephone counseling, and the association between tobacco use and COVID-19. During the trial, Quitline counselors were able to facilitate NRT for participants at no cost.

Trial Design

Trial Design Overview

The study design is a two-arm randomized controlled trial of 600 participants (300 participants in the intervention group and 300 in the comparison group) from Hung Yen province of Vietnam (Figure 1). The intervention group received one-way motivational text messages (seven in the first week, two per week in weeks 2-26) to promote cessation and provide encouragement to access Quitline and free NRT. They also received weekly two-way assessment text messages asking how many times they had smoked tobacco in the past 24 hours and whether they would like to receive a call from the Quitline, which is then provided. The control group received twice-monthly two-way assessment text messages asking how many times they have smoked tobacco in the past 24 hours. The study is being implemented by the Institute of Population, Health, and Development (PHAD), Hanoi, Vietnam, and is based on a long-term partnership between the Institute and UMMS.

Figure 1. Study scheme. *The intervention group received one-way motivational text messages (seven in the first week, two per week in weeks 2-26) to promote cessation and provide encouragement to access Quitline and free nicotine replacement therapy. They also received weekly two-way assessment text messages asking how many times they had smoked tobacco in the past 24 hours and whether they would like to receive a call from the Quitline, which is then provided. **The control group received twice-monthly two-way assessment text messages asking how many times they have smoked tobacco in the past 24 hours. SEQ-12: 12-item Smoking Self-Efficacy Questionnaire.



Study Setting and Inclusion Criteria

Hung Yen province has a population of about 1.2 million, organized into 10 districts and 161 communes. In Hung Yen province, the vast majority of the residents have a mobile phone. Participants are recruited from four communities (communes) in Hung Yen province: Binh Minh, Viet Hung, Tan Viet, and Bach Sam. Each of the selected communes satisfy the following criteria: (1) have a community health center with a medical doctor; (2) are not currently participating in other studies for smoking cessation; and (3) have a minimum geographic separation of 12 km (7 miles) from all other study communes to minimize possible contamination. To be enrolled in this trial, consenting adult men and women need to fulfill each of the following criteria: (1) be a resident of the selected commune, (2) be a current smoker, (3) be able to receive text and read text (literate), (4) not be cognitively impaired, (5) not be a smoker who helped develop the motivational texts used in the intervention, and (6) not be a family member of another participant in the study. Sex is not an eligibility criterion, but rates of smoking among women are very low in Vietnam; therefore, the sample is likely to be overwhelmingly male.

Recruitment Approach

At the beginning of the study, all study personnel and community and Quitline collaborators were trained carefully about the study protocol and standard operational procedures. Advertising of the study is conducted by health workers at community health centers and community health workers. Recruitment events are held at the commune health center on an approximately monthly basis. Interested individuals are screened for eligibility by study staff, who then explain the

study to them. If they are eligible and willing to participate, they receive further details about the purpose of the research; procedures involved; their right to decline to participate and withdraw from the research at any time; potential risks, discomfort, or adverse effects; prospective research benefits; incentives for participation; and research participants' rights. Participants receive either a token of mobile telephone credit for participating or a basic phone that can be used for texting if they do not have a phone. The participants then sign a consent form and proceeded to the baseline assessment and random assignment. Protocol fidelity is determined by the Vietnam coinvestigators who directly monitor 20% (150/750) of all study enrollment and follow-up visits and complete a fidelity checklist.

Randomization

All participants are told that they will be randomized to either the intervention or the comparison group. The allocation of participants to study arms is based on a permuted block scheme in which treatment assignments are made within blocks so that the numbers assigned to each treatment arm are equal after a block has been filled. Blocks of various sizes (2, 4, and 6) are used in random order to facilitate allocation concealment. At the end of the baseline assessment survey, the research staff enter the participant ID and participant mobile phone number from the survey into our texting system, which references the next allocation within the table and adapts based on the allocation assignment. Using this technique, both participants and research staff are blinded to the allocation during the initial session. The research staff are blinded to allocation when assessing outcomes.

Intervention Condition

Participants who are randomized to the intervention arm receive one motivational text message per day in the first week of the trial and two motivational messages per week for the next 25 weeks. They also receive weekly two-way assessment messages (described above) that ask the participant whether they have smoked recently and if they would like to receive a call from the Quitline. If they say "yes," the Quitline calls the patient and offers counseling and access to free NRT. Participants who are randomized to an intervention condition receive encouragement (eg, motivational texts) and the participants themselves choose whether and when to engage in some levels of the intervention (Quitline, NRT) either by texting back to request a call or by calling the Quitline directly. The advantages of this encouragement design are that it provides an indication of uptake or participation, allowing variability in uptake of intervention components and providing an assessment of intervention reach and effective dose.

Control Condition

Participants who are randomized to the comparison condition receive only a two-way assessment question every two weeks, asking if they have smoked recently. Participants in the comparison group are not specifically being encouraged by the research team to seek Quitline counseling or NRT, but they could proactively seek it from the local clinic or from the Quitline.

Sample Size and Power

Our calculations are based on several assumptions. We have estimated the control cessation rate to be 10% in the comparison group, and based on our prior similar trials, we have derived a 9% difference in intervention and control. With a sample of 600 participants who are randomized 1:1 to the intervention and comparison conditions, we are able to detect a 10% difference between groups (two-sided chi-square test, α=.05) with 91% power. On the basis of previous studies, we estimate that there will be about 15%-20% attrition. Thus, although we require a sample size of 600 participants to complete a 6-month follow-up, we plan to randomize 750 participants at baseline (Figure 1). We will monitor recruitment and retention and inflate our sample as needed to achieve the resulting sample of 600 participants completing the 6-month follow-up.

Data Collection

All patient-facing documents are translated into Vietnamese by a certified and qualified translator. All translators are native speakers of Vietnamese and members of the American Translators Association. Once translated, the documents are edited by an accredited second language expert for readability, terminology, and accuracy. The materials are then proofed for completeness, formatting, and layout. All translated materials receive a certification of accuracy from the translation company.

Baseline data are collected by the research staff during commune-based enrollment events. Baseline data collection includes patient demographics, comorbidities, technology use, and Quitline use. Participants are asked about their level of readiness to quit (response options: not thinking about quitting, thinking about quitting, setting a quit date, quitting smoking today, and having already quit smoking), former quit attempts, and current smoking habits (how many cigarettes smoked per day, other tobacco products used, how soon after they smoke, how old they were when they first smoked, and how many years they smoked every day). Participants are asked how many of their immediate family members, extended family members, close friends, friends, acquaintances, and coworkers smoke. Social support for quitting is measured using the shortened partner interaction questionnaire [11] for those who are married or partnered. Smoking cravings are assessed using the brief 10-item version [12] of the Questionnaire of Smoking Urges [13], which retains the two-factor structure of the original and has high internal consistency [12]. At baseline, we also administer the 12-item Smoking Self-Efficacy Questionnaire (SEQ-12) [14], a questionnaire with two subscales measuring confidence in the ability to refrain from smoking when facing internal and external stimuli, respectively. The scale has high test-retest reliability and is predictive of future cessation, and the subscales have good internal consistency [14].

Study Outcomes

The primary outcome of the study is the tobacco cessation rate at 6-month follow-up. At the follow-up research visit, the research staff determines current smoking through self-report based on the following question, "Do you currently smoke tobacco (smoked even 1 puff of tobacco in the last 7 days)?" (yes or no), and then verify with a carbon monoxide breath

monitor. Patients who respond "no" to smoking are now classified as nonsmokers if their carbon monoxide measurement is less than 10 ppm [15]. Secondary outcomes are changes from the baseline in self-efficacy on the SEQ-12 and Quitline use. We will also report on follow-up measurements of the Brief Questionnaire on Smoking Urge, NRT use, details of quit attempts, and smoker perceptions of the intervention. Attendance at follow-up events is encouraged by community health workers, and those who do not appear are offered the opportunity to complete the measures by telephone. In similar studies in this region, retention has been very high.

Throughout the 6-month participation period, we will collect additional assessment data through the assessment texts, including measures of abstinence assessments, and interest in and use of the Quitline. Quitline staff record details of intake assessment (number of calls, smoking status, and method used to quit if applicable) and fidelity of follow-up call completion. They also document referrals for the NRT. Data are entered into a secure data management system, with double-data entry occurring on a subset of participants to ensure accuracy or data entry.

Adherence and Monitoring

Given that the intervention is low-risk, participants are unlikely to be withdrawn from the trial on the basis of safety concerns. Participants may withdraw at their own request. Participants are free to engage in other smoking cessation-related care and interventions during their participation. A number of actions are being taken to monitor and ensure adherence to intervention protocols. Research staff are trained on responsible conduct of the research. Consent materials are uploaded to a secure data capture system and reviewed by the project director. A sample of 20% (150/750) of enrollments are monitored by the site principal investigator, who then completes an adherence checklist. For the texting system, the programmer can monitor the texts being sent and received.

Data Analysis

All primary analyses will be conducted on an intention-to-treat basis. However, secondary analyses will explore dose-response effects among those with variable levels of adherence to the intervention. All analyses will be two-sided, and the α error will be set at .05. We begin the statistical analysis by examining the univariate statistics and distributions. We will examine the balance of participant characteristics by study groups and account for any imbalances in our multivariable analysis. As appropriate, group differences will be tested using chi-square tests of independence, Z-test or *t* test (two-tailed), or the equivalent nonparametric tests depending on the distribution of the variables. In accordance with best practice, differences in baseline characteristics of the intervention and comparison groups will be established based on standardized differences rather than on tests of statistical significance [16,17].

The primary outcome was the patient tobacco cessation rate (quit rate) at 6 months follow-up visit and will be compared using a two-sided chi-square test. We will include a multivariable logistic regression model to adjust for any potential confounding factors, if needed. As a secondary outcome, we will compare self-efficacy between intervention and control conditions: means on the SEQ-12 (and its subscales) will be compared between the intervention and control groups over time using repeated-measures analysis of variance and Student *t* test. A generalized linear model for repeated measures will be used to adjust for potential confounding factors, if needed. There are no planned interim analyses, but they may be requested or approved by the Data Safety and Monitoring Board.

Ethics and Confidentiality

The study has been approved by the institutional review board (IRB) at the UMMS (H00012953) and the Institute of Population, Health and Development, Vietnam (PHAD-2017/M2Q2-01). All important protocol modifications are approved by the IRB and registered with ClinicalTrials.gov. Research assistants provide a brief overview of the study, including the reason the study is being performed, a description of the study design, and the participant's role in the investigation if he or she decides to participate. The participant is informed of the potential benefits of the study. The patient is also informed that the design of the study requires collection of personal identifiers of the safeguards in place to protect that information, and of his or her right to withdraw from the study at any time (at which point all personal identifier data collected will be destroyed). All participants provided written informed consent for study inclusion, administration of surveys, and carbon monoxide verification. At any time, participants may withdraw their consent.

All data are obtained by trained study staff and entered directly into electronic forms on a secure website designed for this purpose. We have created a texting service that is responsible for sending text messages, as well as receiving the assessment text responses (ratings and time to first quit). The software program we developed uses a secure application programmable interface to forward the patient's phone number and send and receive the texts. The motivational messages do not contain any personal health information, and the texting service does not store the phone numbers (phone number data are not transferred to any site outside of Vietnam). Participants are informed of the potential risk of confidentiality of sending and receiving text messages during the informed consent process.

Participants are identified with a study number: the key is located centrally and securely and is accessible only to certified study personnel on an as-needed basis. All patient contact, including consent, interviews, and all study procedures with human subjects occurred onsite in Vietnam. All data are deidentified according to Health Insurance Portability and Accountability Act (HIPAA) standards before transfer to the investigators and staff for analytical purposes. Personal identifiers are abstracted onto separate confidential forms and are not transferred outside Vietnam. All records consisting of personal identifiers will be destroyed upon completion of the study. The data are stored in a HIPAA-compliant regulated environment and access will be only through a secure virtual private network. All the related identifiers of the participants are encrypted in the database.

Safety and Adverse Events

As this trial is a phase 3 study including NRT and our behavioral intervention, we have established a Data and Safety Monitoring Board (DSMB). The DSMB is charged with reviewing protocols and consent documents for this trial, monitoring safety issues throughout the study, and the quality of the accumulating data, providing guidance on interim analyses and stopping rules. The DSMB comprises persons with no direct involvement in the study or conflict of interest with the research team conducting the randomized trial and has the authority to halt the trial as needed.

Participants who call the Quitline may receive over-the-counter NRT in the form of nicotine lozenges at 4-mg doses. The risk of NRT has been evaluated in detail: as this treatment has less nicotine than cigarettes, it is in general a risk reduction from active smoking. All participants who had a Food and Drug Administration contraindication to nicotine lozenge are excluded. Patients may become uncomfortable when asked about psychosocial factors such as smoking cravings or urges and are reminded repeatedly that they are under no obligation to respond to any question, and interviewers are trained and supervised in appropriate interview techniques. The principal investigator monitors all adverse events; all adverse events, both serious and nonserious, are summarized in the report to the IRB committee for annual study review and renewal.

Patients are given up to 6 weeks of NRT if requested during the study period, and free NRT is not maintained beyond the study period; participants revert back to usual care at their community health centers after the end of their involvement in the study. Participants in the comparison condition are allowed (but not actively encouraged or facilitated) to engage with the Quitline if they choose.

Results

Intervention Development and Adaptation

After existing candidate messages were professionally translated to Vietnamese, 14 consultants (former smokers who had used the Bach Mai Quitline services) and 7 professionals (5 counselors and 2 doctors from the Bach Mai Quitline) reviewed the 126 existing messages and were asked to identify messages that they liked and disliked. Reconciling the two sets of messages through a group review, there were 20 text messages that were disliked by none of the consultants or Quitline counselors, and these were identified for inclusion in the message pool. The message writing exercise with 10 former smokers led to the creation of 238 new smoker-written messages. After eliminating messages that were incomplete, unclear, or clearly redundant, a set of shortlisted messages was reviewed independently by researchers for preference and the top 44 messages were identified for inclusion in the message pool. Between the expert-written messages and the smoker-written messages, a total of 57 messages were selected for the intervention: seven messages to be sent during week 0 of the intervention, and two messages per week to be sent during weeks 1-25 of the intervention. The messages reflected several themes: calling the Quitline and Quitline as helpful, knowledge and health risks, self-efficacy and motivators, role of family, and quitting tips. The final messages were reviewed by a researcher who sequenced them using a social cognitive approach, for example, messages related to knowledge and health risks occurred earlier in the sequence and quitting tips occurred later in the sequence. The following are examples of motivational text messages received by the intervention group. The text messages were translated from Vietnamese and the original text can be found in Multimedia Appendix 1.

- “The following message was written by a smoker in your community...I felt like the counselors at the Bach Mai Quitline are close as family members, who want to help me to quit smoking.”
- “The following message was written by a tobacco cessation expert...Most people make repeated quit attempts before they are successful. You can succeed. Your doctor is available with treatment options and support to help you.”
- “The following message was written by a smoker in your community...Thinking about my family, my children, my grandchildren and people helped me stay focused on quitting.”

Trial Status

The study was funded in August 2017. The study was reviewed and approved by the University of Massachusetts Medical School IRB in 2017. Recruitment began in November 2018. As of March 2021, 750 participants have been recruited from four communes, and a total of 700 (93.3%) participants completed the follow-up. An analysis of the trial results is in progress; results are expected to be published in late 2022.

Discussion

Summary

Mobile health Messaging to Motivate Quitline Use and Quitting (M2Q2) will examine whether a motivational text messaging intervention is effective in promoting cessation and treatment uptake among Vietnamese smokers. It is a unique opportunity to engage a challenging population of rural Vietnamese smokers in a novel intervention. This study examines the effectiveness of a culturally tailored text messaging intervention to motivate tobacco cessation and connect smokers to underused Quitline and NRT.

Limitations

This study has several limitations. First, the study applies randomization at the individual level, allowing for ample power and a rigorous approach; however, it is possible that the close-knit nature of these rural communities causes participants to share information during the follow-up period, resulting in unintentional unblinding to allocation and contamination. Second, the global COVID-19 pandemic occurred during the trial, and Vietnam adopted stringent infection control measures in response. Recruitment was paused for a matter of weeks, but our original targets and retention rates did not appear to have been profoundly affected. COVID-19 rates were relatively low in Vietnam, but we will still test the potential confounding effect of the pandemic in our analyses, given the potential effect of COVID-19 on cessation rates in the comparison group. Finally, the study is limited to a moderate follow-up period of 6 months,

rather than a longer follow-up period. In conclusion, this study examines the effectiveness of potential mobile health interventions that can be implemented nationwide in Vietnam and in other diverse populations that bear significant burdens from smoking.

Dissemination Plan

We will present our work at relevant scientific conferences and publish our results in peer-reviewed literature. Manuscripts and other products arising from the study will be produced by the research team and will not involve professional writers. In line with guidelines from the International Committee of Medical Journal Editors, authorship will be contingent on the following criteria:

- Substantial contributions to conception and design, or acquisition, analysis, or interpretation of data
- Drafting of the study or critical revision for important intellectual content
- Final approval of the version to be published
- 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 article are appropriately investigated and resolved

In conclusion, mobile interventions for smoking cessation in low- and middle-income countries have been shown to be feasible and acceptable [18,19]. We anticipate that the culturally tailored M2Q2 intervention will promote tobacco cessation and treatment uptake in smokers in Vietnam.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Examples of motivational text messages received by the intervention group.
[PDF File (Adobe PDF File), 43 KB - resprot_v10i10e30947_app1.pdf]

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Abbreviations

DSMB: Data and Safety Monitoring Board
IRB: institutional review board
NRT: nicotine replacement therapy
SEQ-12: 12-item Smoking Self-Efficacy Questionnaire
UMMS: University of Massachusetts Medical School

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Protocol

Using Electronic Health Record–Based Clinical Decision Support to Provide Social Risk–Informed Care in Community Health Centers: Protocol for the Design and Assessment of a Clinical Decision Support Tool

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Abstract

Background: Consistent and compelling evidence demonstrates that social and economic adversity has an impact on health outcomes. In response, many health care professional organizations recommend screening patients for experiences of social and economic adversity or *social risks*—for example, food, housing, and transportation insecurity—in the context of care. Guidance on how health care providers can act on documented social risk data to improve health outcomes is nascent. A strategy recommended by the National Academy of Medicine involves using social risk data to adapt care plans in ways that accommodate patients' social risks.

Objective: This study's aims are to develop electronic health record (EHR)–based clinical decision support (CDS) tools that suggest social risk–informed care plan adaptations for patients with diabetes or hypertension, assess tool adoption and its impact on selected clinical quality measures in community health centers, and examine perceptions of tool usability and impact on care quality.

Methods: A systematic scoping review and several stakeholder activities will be conducted to inform development of the CDS tools. The tools will be pilot-tested to obtain user input, and their content and form will be revised based on this input. A randomized quasi-experimental design will then be used to assess the impact of the revised tools. Eligible clinics will be randomized to a control group or potential intervention group; clinics will be recruited from the potential intervention group in random order until 6 are enrolled in the study. Intervention clinics will have access to the CDS tools in their EHR, will receive minimal implementation support, and will be followed for 18 months to evaluate tool adoption and the impact of tool use on patient blood pressure and glucose control.

Results: This study was funded in January 2020 by the National Institute on Minority Health and Health Disparities of the National Institutes of Health. Formative activities will take place from April 2020 to July 2021, the CDS tools will be developed between May 2021 and November 2022, the pilot study will be conducted from August 2021 to July 2022, and the main trial will occur from December 2022 to May 2024. Study data will be analyzed, and the results will be disseminated in 2024.

Conclusions: Patients' social risk information must be presented to care teams in a way that facilitates social risk–informed care. To our knowledge, this study is the first to develop and test EHR-embedded CDS tools designed to support the provision of social risk–informed care. The study results will add a needed understanding of how to use social risk data to improve health outcomes and reduce disparities.

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KEYWORDS

social determinants of health; decision support systems, clinical; electronic health records; community health centers; health status disparities

Introduction

Background

The conditions in which people live, work, and play—known as social determinants of health (SDH)—have well-documented impacts on health care access and quality and also on health outcomes [1-3]. SDH are shaped by broader social, economic, and structural forces and contribute to long-standing, avoidable health disparities and inequities [2]. Given the growing recognition of the impact of SDH on health, many health and health care professional organizations (eg, the American College of Physicians and the National Academy of Medicine) now recommend systematically screening for and documenting patients' experiences of social adversity, including social risk factors related to food, transportation, and housing insecurity, in electronic health records (EHRs) [4-8]. As social risk data become more available in EHRs, it is important to understand how care teams can use this information to improve patient outcomes, which might reduce related health inequities.

A 2019 National Academies of Sciences, Engineering, and Medicine [9] report on integrating social and medical care describes a range of uses for reported social risk data in clinical settings. One such use is to provide or link patients with reported social risks to relevant social services, such as providing food resources to food-insecure patients or otherwise targeting social risks within the context of care delivery (*social risk–targeted care*). The National Academies of Sciences, Engineering, and Medicine report also describes a category of interventions that use social risk data to adapt care plans to account for a given patient's social risks (*social risk–informed care*) [10]. Research on *social risk–targeted care* suggests that linking patients with social needs to specific social services can improve health outcomes [10-13]. Far less is known about the adoption and impact of social risk–informed care, although such care plan adaptations might improve health for individual patients and contribute to reducing disparities in care outcomes. For example, a social risk–informed care plan adaptation for a patient experiencing homelessness might involve avoiding refrigerated medications; for a patient with diabetes and food insecurity, it might include modifying insulin doses based on monthly food benefit schedules [14,15]. A series of studies in the Veterans Health Administration system found higher rates of positive clinical outcomes associated with social risk–informed care plan adaptations [16-20]. However, care that incorporates information about patients' social context is not systematically incorporated into chronic disease management. Previous research found that social risk–informed care occurs only 15%-22% of the time in diverse care settings [21,22].

Social risk information must be presented to care teams in a manner that is useful to them and does not disrupt clinical workflows to encourage the systematic delivery of contextualized, social risk–informed care. Numerous studies have shown that clinical decision support (CDS) tools embedded in EHR systems can enhance care quality by providing clinical information to care teams along with suggestions on evidence-based actions relevant to a given patient's care [23-29]. Such tools can include reminders about overdue screenings, summaries of a given patient's health risks, and care recommendations per current guidelines. However, to our knowledge, the use and impact of EHR-based CDS to support the provision of contextualized, social risk–informed care has not been assessed.

Objectives

This paper describes the protocol for a National Institutes of Health (NIH)-funded study (COHERE; Contextualized Care in Community Health Centers' Electronic Health Records; R01MD014886) designed to develop and test CDS tools that present care team members with a given patient's social risk information and both recommend and facilitate care plan adaptations based on those risks. This study will test the hypothesis that providing CDS that alerts care team members to patients' known social risks and recommends relevant care plan adaptations will result in improved health outcomes. This study's focus is on hypertension and diabetes control; however, the results will have implications for a wide range of morbidities.

Methods

Setting

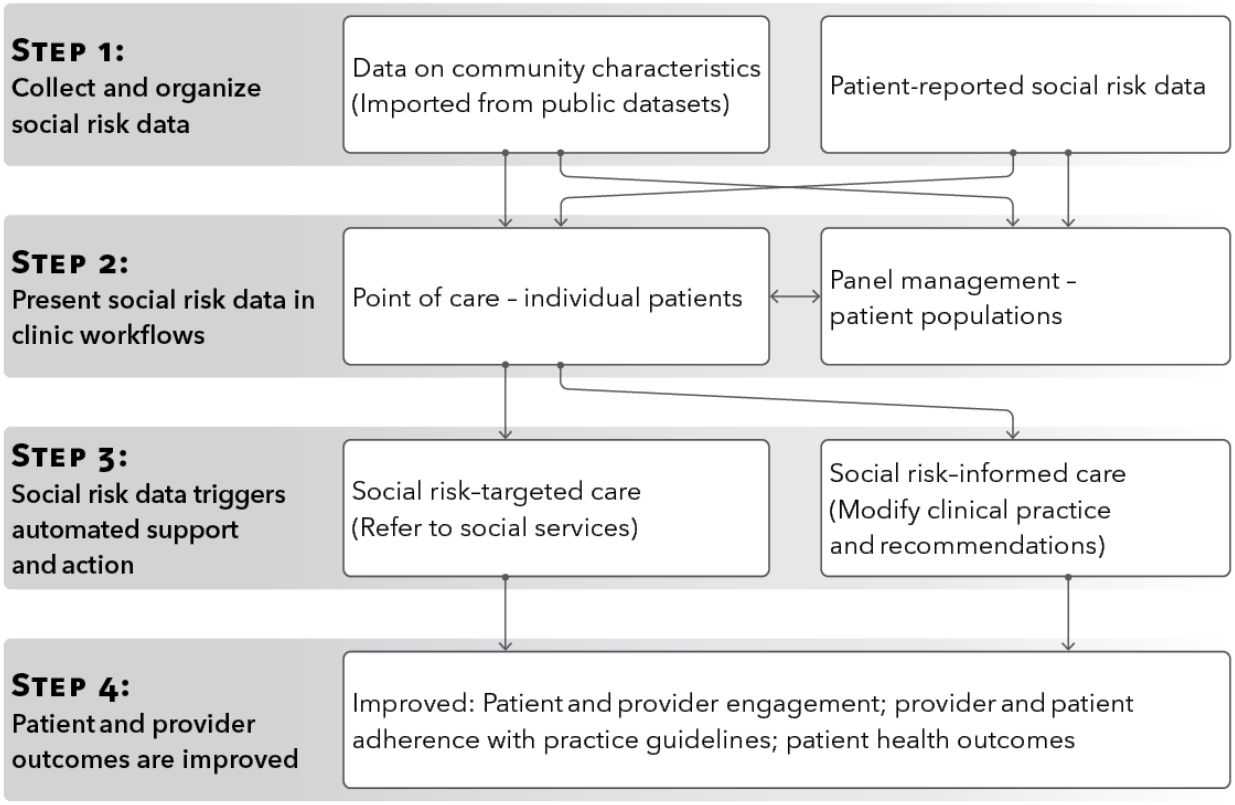
The study will be conducted among community health centers (CHCs) that are members of OCHIN (not an acronym). OCHIN is a nonprofit health center–controlled network that hosts a single Epic EHR for >600 primary care CHCs located across the United States. As part of previous NIH-funded studies (1R18DK105463 and 1R18DK114701) and OCHIN's ongoing CHC-centric EHR modifications, a suite of EHR tools was designed to enable documentation of social risk data and the provision of related referrals [23,30-33]. These tools were activated OCHIN-wide in June 2016; as of April 2021, >700,000 social risk screening results in >400,000 unique patients have been documented using these tools. The tools were adapted as their implementation was based on user input and to ensure alignment with the Epic EHR's 2018 social determinants module. At present, the tools enable users to flag targeted patients for social risk screening, select from several screening tools (Protocol for Responding to and Assessing Patients' Assets, Risks, and Experiences; the Centers for Medicaid/Medicare Services' Accountable Health Communities screening tool; social risk questions from the Institute of Medicine [now the National Academy of Medicine]; or individual social risk domains) [34-37], enter patient-reported social risk data via several interfaces, and allow patients to self-enter data through the patient portal or at the point of care. The tools can also be used to document patients' priorities

related to social needs and interest in related referrals. In the trial described here, the CDS tools to be developed and tested will draw information on patient-reported social risks from data documented through these existing tools.

Conceptual Guide

The conceptual framework proposed by DeVoe et al [38] for integrating SDH into primary care practice will guide the design of this intervention. A modified version of this framework (Figure 1) shows that data on self-reported social risks can be used to affect health care quality and outcomes either through panel management (eg, focused outreach) or at the point of care of individual patients through social risk–targeted care and social risk–informed care. This study focuses on EHR tools designed to facilitate point-of-care applications for social risk data, which have been proposed in theory but never formally tested.

Figure 1. Social risk data and targeted or informed care (adapted from DeVoe et al [38]).



Study Design

A randomized quasi-experimental design will be used to assess the impact of the newly developed CDS tools designed to support social risk–informed care. Before beginning the main trial, several formative activities and a pilot study will be conducted.

Formative Phase

First, potential care plan adaptations will be drawn from a systematic scoping review of social risk–informed care recommendations included in national hypertension and diabetes guidelines and our team's prior research. Second, diverse CHC staff and patients will be asked to review and prioritize potential care adaptations. CHC staff will be invited to provide input through a stakeholder committee, whereas patients will be engaged using OCHIN's established patient engagement panel. This process will help the research team determine (1) which social risks the study's CDS tools will include, (2) the specific content of the CDS tools, and (3) the preferred form in which the CDS tools should appear in the EHR. The tools will then be pilot-tested for 12 months in three CHCs and further refined based on extensive user feedback from these pilot sites. Figure 2 outlines our process for developing the tools in preparation for the main trial.

Figure 2. Steps involved in developing the clinical decision support tools. CDS: clinical decision support; CHC: community health center; EHR: electronic health record; NASEM: National Academies of Sciences, Engineering, and Medicine; SDH: social determinants of health [39,40].

Step 1: Identify potential care plan adaptations.	Step 2: Obtain CHC staff and patient perspectives about the care plan adaptations identified in Step 1 and the CDS tools' form and functions in the EHR.	Step 3: Develop first version of the CDS tools.	Step 4: Obtain input on the structure and appearance of the CDS tools.	Step 5: Pilot test the CDS tools.	Step 6: Refine the CDS tools based on pilot test results.
Conduct a systematic scoping review of social risk–related care plan adaptations listed in national hypertension and diabetes care management guidelines. • Apply a PubMed search strategy targeting hypertension and diabetes clinical guidelines. • Review abstract citations for exclusion. • Apply SDH search terms to full text guidelines to identify relevant SDH sections. • Code and extract social risk-related excerpts using NASEM's 5A framework [9].	• Convene stakeholder committee (SC) comprised of diverse CHC staff (eg nurse care managers, provider builders, clinicians, behavioral health clinician leads, clinical pharmacists, and population health coordinators). • The SC will meet iteratively to share their perspectives on tool content. • SC members will also participate in one-on-one interviews about using social risk information in clinical decision-making; they will review vignettes [39,40] based on real patients and will be asked to discuss how they would make decisions in the situations presented. • Conduct two meetings with 15 CHC patients, who regularly give input on research at OCHIN, to obtain feedback on potential care plan adaptations based on social risks and offer further adaptation suggestions.	Consider evidence on the qualities of effective CDS tools in parallel with user input, to ensure optimization of the tools [27,28].	Present mocked-up tools to CHC staff at OCHIN's Clinical Operations Review Committee (CORC), comprised of dozens of clinical leaders from OCHIN's member CHCs, three times over 3 months to iteratively determine how and where the tools should appear in the EHR to optimize usability.	• Activate the tools in three CHCs recruited based on their social risk screening rates. • Orient clinic staff on-site or remotely. • Track tool use in the pilot CHCs (eg how often the hyperlink to suggested care plan adaptations was selected, how often suggested adaptations are enacted). • Obtain user input on the tools through interviews with pilot clinic staff and two webinars where staff from all three pilot clinics discuss the tools.	Revise tool content, form, and associated training processes, as indicated.

Main Trial

Intervention clinics will have the CDS tools turned on in their EHR and will be followed for 18 months to assess (1) tool adoption, (2) the extent to which tool suggestions are enacted by care team members, and (3) the impact of tool use on two national clinical quality measures (CQMs) [41]: blood pressure control and hemoglobin A_{1c} (HbA_{1c}) control. We will also assess care team members' perceptions of the tools' usability and impacts on care quality and patient-provider interactions.

Randomization and Recruitment

All OCHIN clinics that provide primary care and have documented ≥200 social risk screenings (excluding the pilot clinics) will be identified. It is anticipated that approximately 60 clinics will meet these criteria. Eligible clinics will be randomized 1:1 to 1 of 2 groups: potential intervention or control. Clinics from the potential intervention group (n=30) will be recruited in random order until 6 agree to participate. In the study analyses, outcomes in these 6 intervention clinics will be compared with those in the control clinics (n=30). This approach allows for randomization between the intervention and control arms while eliminating the recruitment of CHCs to a study where some will receive no intervention (ie, only clinics that will receive the intervention will be contacted for recruitment). This method is possible as all OCHIN member CHCs agree that their EHR data may be used in research as part of their membership agreement.

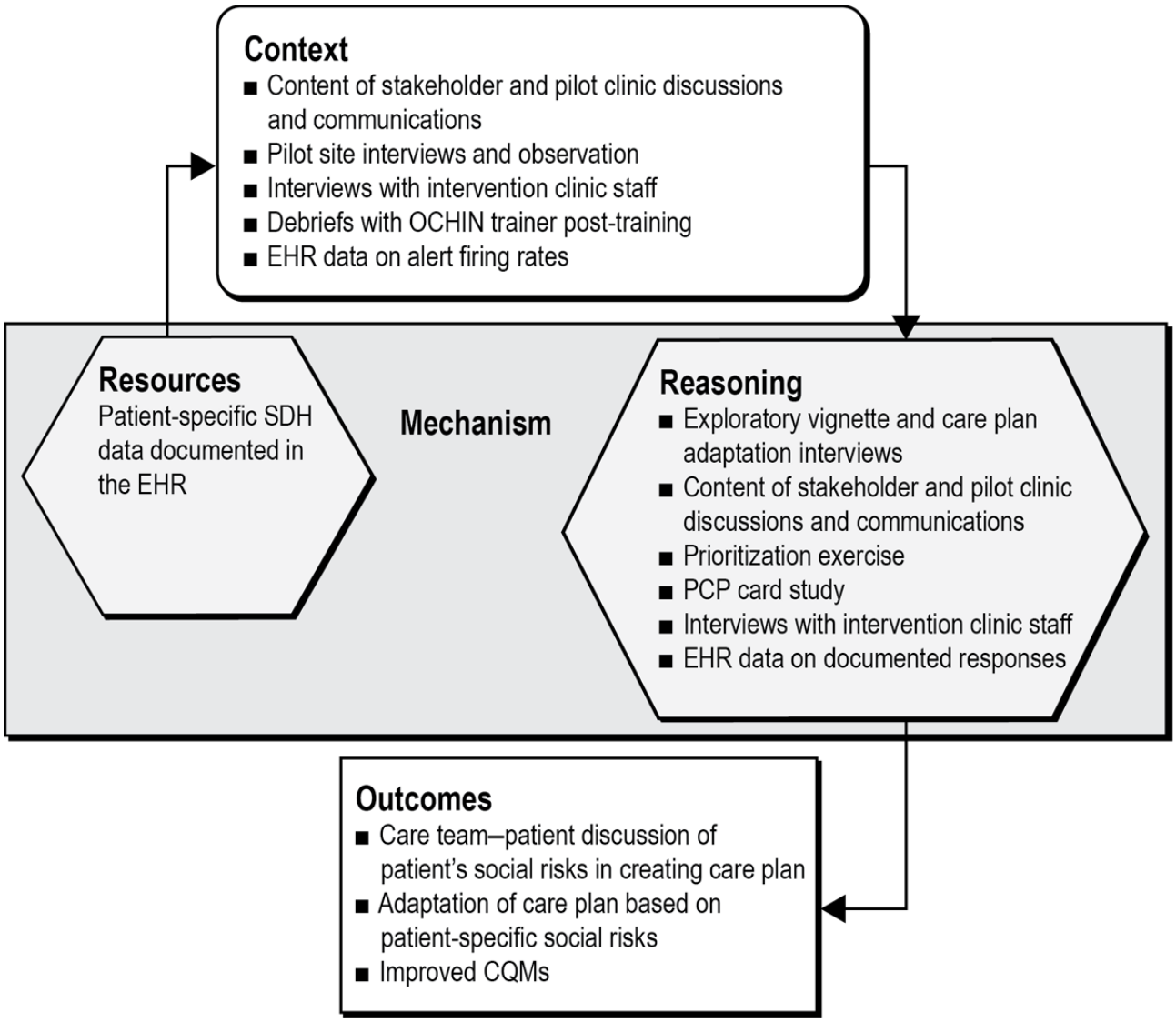
Intervention

Shortly before the tools are activated in participating CHCs, clinic staff members will be oriented to the CDS tools by an OCHIN EHR trainer (either on-site or remotely). Clinic staff will be offered a series of structured, sequenced activities using training materials developed by the study team in collaboration with the trainer. This will be the only form of implementation support offered to the main trial clinics as we seek to assess the adoption and impact of the CDS tools in a real-world situation.

Analytic Framework

Mixed methods will be used to assess tool adoption and impact within a realist framework designed to identify what works, for whom, and in what circumstances [42,43]. The realist approach focuses on the context-dependent causal pathways through which an intervention (here, the CDS tool) produces outcomes (here, primarily adaptation of care plans based on patient-specific social risks and improved CQMs; Figure 3).

Figure 3. Realist evaluation framework. Resources: the resource or resources offered by the program under study. Context: pre-existing individual, social, institutional, economic and system-level values, norms, and relationships in which interventions are introduced. Reasoning: reasoning and reaction of stakeholders in response to resource or resources. Outcomes: intended and unintended changes resulting from the intervention. CHC: community health center; CQM: clinical quality measure; EHR: electronic health record; PCP: primary care provider; SDH: social determinants of health.



Data

All quantitative data will be extracted from OCHIN's Epic EHR; these data are centrally managed and quality checked [44-46]. Qualitative data for the intervention phase will be collected via semistructured interviews with diverse clinic staff who interface with the CDS tools during patient care (eg, providers, care managers, and medical assistants) and an EHR-embedded provider card study at each study site. The interviews will explore relevant clinical contexts, perceptions and use of social risk data and CDS tools in clinical encounters, and the impact of patient-reported social risk data on clinical decision-making, quality of care, and patient-provider interactions, including potential negative impacts of tool use. Card studies are short (<1 minute) surveys designed to obtain point-of-care data on clinical decision-making [47]. This card study, which will be embedded within the EHR and, therefore, the provider workflow, will be used to assess provider reactions to and actions taken based on patient-reported social risk data.

Quantitative Analyses

We will describe the percentage of clinic encounters at which (1) the CDS tools appeared to users at the intervention clinics, (2) users reviewed tool suggestions, and (3) the suggested care plan adaptations were enacted.

The primary trial outcomes are changes in the two CQMs expected to be affected by social risk–informed care: blood pressure control and HbA_{1c} control. Each CQM's denominator will be defined according to which patients are eligible for that measure at the time of a clinic visit (eg, patients with diabetes are in the HbA_{1c} measure denominator) per national CQM measurement specifications [41]. Two-level hierarchical linear models [48-50] will be used to assess the impact of CDS tools on these outcomes. As these outcomes are binary, the generalized form of the hierarchical linear model with a log link and binomial distribution will be used. Textbox 1 shows other potential covariates; this list will be finalized based on the extent to which person-level covariates were balanced between the final intervention and control arms and will be included in the

first level of the model representing the person level. The second level of the model, the CHC level, will include arm as an independent variable (control vs intervention) and a random effect for the intercept (ie, intercept-as-outcomes model). Population-averaged marginal proportions and associated 95% CIs will be calculated by arm, along with the difference between those proportions (ie, the marginal effect) and the associated 95% CI that incorporates the random effects (ie, differences between CHCs) and any included covariates.

In secondary analyses, a repeated cross-sectional design will be used to assess the differential changes in the outcomes across time. A panel design is impractical in this population of CHC patients, so using repeated measures would result in a selective (eg, patients with stable and continuous care) and smaller sample. As we will be able to collect up to 18 months of data, we will subset the relevant patient subpopulations within clinics in 6-month increments and model time as a between-subjects effect in the model described above to evaluate the effectiveness for each outcome. More specifically, we will add time (6, 12, and 18 months) and the product of time and arm that represents their interaction in level 2 of the model. We will then calculate the population-averaged marginal proportions and associated 95% CIs by arm and time points, along with the marginal effects between arms within time points and between arms across pairs of time points (ie, differences-in-differences). Significant marginal effects between arms across time would suggest a differential change between the arms across time. As all secondary CQM outcomes (Textbox 1) are also binary, we will use the same approach to evaluate between-arm differences on these outcomes as for the primary outcomes.

Intent-to-treat analyses will be used to establish effectiveness at the population level and per-protocol analyses to assess the impact of the tools when used. For the primary analysis, depending on the size of the intraclass correlation (between 0.01 to 0.05), this study has at least 80% power to detect a 9%-17% difference in blood pressure control (n=343 per CHC; assuming baseline level of 60% blood pressure control calculated from OCHIN data) and a 10%-18% difference in HbA_{1c} control (n=214 per CHC; assuming baseline level of 34% HbA_{1c} control calculated from OCHIN data) between the intervention and control groups at a two-tailed α level of .05.

Textbox 1. Primary and secondary analysis variables.

Primary outcomes

- Controlled blood pressure (<140/90)
- Controlled hemoglobin A_{1c} (in diabetes mellitus: <9%)

Secondary outcomes

- BMI ≥25 (adults; not a formal clinical quality measure: a health outcome associated with clinical quality measure)
- Controlled lipids (not a formal clinical quality measure: a health outcome associated with clinical quality measure)
- BMI screening and follow-up (adults)
- Lipid therapy (coronary artery disease)
- Use of aspirin or antithrombotic (ischemic vascular disease)

Potential covariates

- Patient covariates: Age, gender, race and ethnicity, primary language, poverty level, insurance status at a visit, and number of visits to that site or provider in last year (care use)
- Patient comorbidities: Charlson comorbidity score (modified)—an indicator of serious comorbid conditions that may shorten life expectancy
- Visit type:
  - In-person, telephone, and virtual
  - Outreach, encounter
- Provider type:
  - Degree (eg, medical doctor, registered nurse, or physician assistant)
  - Prescribing privileges (yes or no)
  - Number of patients in panel

Qualitative Analyses

Consistent with the constant comparative method, analyses will be iterative and inductive. Emergent understandings will be explored in subsequent data collection [51]. An immersion-crystallization process [52], which entails multiple iterations of data immersion, reflection, and code development and application, will be used to identify themes and patterns in the data [53].

Mixed Methods Realist Analyses

A convergent comparative *case analysis* approach will be used [54], where qualitative and quantitative data build an understanding of the change process in each *case* (clinic). Quantitative and qualitative data will be integrated, as shown in Figure 3. Data from each case will be *merged* for analysis and then compared within and across clinics to confirm, expand on, or challenge each site's findings. Potential context-mechanism-outcome configurations [55-58] will be proposed and then refined as analysis continues to identify context-specific components that enable the use of patient-specific social risk data in adapting treatment plans. Emphasis will be placed on factors influencing the use of patient-specific social risk data in care decisions, including the use of CDS tools, any unintended negative impacts on care processes and outcomes, and patient-provider interactions. Analyses will also explore staff and patient perceptions of how patients' social risk data affect care and the potential to induce or obviate bias when such actions occur.

Results

This project was funded by the National Institute on Minority Health and Health Disparities of the NIH in January 2020. The formative phase started in April 2020 and will run through July 2021. The tool build process began in May 2021 and will continue through November 2022. Most of the tool development activities occurred during the first 3 months, with additional refinements occurring over subsequent months. The pilot study, which is part of the tool development period, will take place between August 2021 and July 2022. The main trial will begin in December 2022 and conclude in May 2024; qualitative interviews and a provider card study will be conducted during this time frame. Data analysis and dissemination activities will take place between December 2023 and November 2024.

The Kaiser Permanente Northwest institutional review board reviewed the study protocol and provided approval for pilot study activities in March 2021. The institutional review board will review the protocol again before the main trial. No research with human subjects will be conducted until the proper approvals have been received.

Discussion

Principal Findings

Although CHCs and other primary care providers are increasingly systematizing social risk documentation, their clinical teams lack guidance on how to use these data to improve patient health and reduce inequities [30,32,59-61]. Referring patients with social risks to needed social services is associated with improved health outcomes and decreased costs [10-13,21,62-80]. Although some of these impacts may occur because social service referrals reduce social risks, recent studies have shown that health improvements subsequent to social service referrals were not mediated solely by changes in social risk status [10,81]. Little is known about how to support social risk–informed care in CHCs or other primary care settings; however, research shows that when social risk data are presented without specific care recommendations, providers use these data inconsistently [22,82,83].

CDS tools in EHRs (eg, alerts, overviews, and care gap summaries) are widely available and can enhance care quality and patient satisfaction, especially when developed with user input [24,25,27-29,84-91]. These functionalities might enhance social risk–informed care; however, we know of no prior studies examining their use in this context. This trial will address this knowledge gap by developing and testing CDS tools that suggest social risk–informed care adjustments. The CDS tools that will be tested will be developed and revised with extensive provider and patient stakeholder inputs. These tools will be designed to enable transferability to any site using the Epic EHR; general principles of using social risk data CDS for social risk–informed care will be disseminated so that similar tools can be built in any EHR system.

Limitations and Considerations

This pragmatic trial will be conducted in CHC settings as CHCs serve patients with high rates of social risks, so study findings may not be fully generalizable to other care settings. Although the recruited CHCs will have documented social risks for ≥200 patients, few will have screened all their patients for social risks, and some will not have endorsed social risks. As a result, these tools may not be relevant to all patients. For addressing this, primary analyses will be limited to patients with known social risks, and differences between these patients and those with no social risk data will be described. Only 1-2 hours of training will be provided as implementation support to the study CHCs; more hours of training might be optimal but would not reflect real-world practices. Finally, this research was conducted in the peri-COVID period; its generalizability must be interpreted in light of the pandemic's effects on patients' health care access and financial security, as well as the changes it spurred in the health care sector around social care delivery [92]. The extent to which pandemic-related changes will endure is not yet clear.

Conclusions

There are no known prior studies assessing whether and how EHR-based CDS can be used to support contextualized social risk–informed care. We believe this study will be the first to develop and test CDS tools that both highlight CHC patients' social risks and suggest care plan adaptations based on reported social context. The tools will be developed with extensive input from CHC staff and patients to ensure patient and provider usability and acceptability. The results will yield usable data for CHCs and other primary care providers to inform strategies that can ensure new social risk screening initiatives translate to improvements in care delivery and health outcomes.

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Authors' Contributions

R Gold conceptualized the work, designed the study, and substantively revised the manuscript. CS contributed to the design of the study (postaward), drafted the initial manuscript, and substantively revised the manuscript. DH contributed to the design of the study and substantively revised the manuscript. AB contributed substantially to the conceptualization and design of the study. EC made substantial contributions to the conception and design of the study. NY substantively revised the manuscript. MP contributed to the design of the study (postaward) and substantively revised the manuscript. R Gunn contributed to the design of the study (postaward) and substantively revised the manuscript. ML helped design the quantitative evaluation components and substantively revised the manuscript. LG conceptualized the work, designed the study, and substantively revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Aside from the grant funding reported above, the authors declare that they have no conflicts of interest.

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Abbreviations

CDS: clinical decision support
CHC: community health center
COHERE: Contextualized Care in Community Health Centers' Electronic Health Records
CQM: clinical quality measure
EHR: electronic health record
HbA_{1c}: hemoglobin A_{1c}
NIH: National Institutes of Health
SDH: social determinants of health

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Protocol

Kinesiotherapy With Exergaming as a Potential Modulator of Epigenetic Marks and Clinical Functional Variables of Older Women: Protocol for a Mixed Methods Study

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Abstract

Background: Kinesiotherapy is an option to mitigate worsening neuropsychomotor function due to human aging. Moreover, exergames are beneficial for the practice of physical therapy by older patients. Physical exercise interventions are known to alter the epigenome, but little is known about their association with exergames.

Objective: We aim to evaluate the effects of kinesiotherapy with exergaming on older women's epigenetic marks and cognitive ability, as well as on their clinical functional variables. Our hypothesis states that this kind of therapy can elicit equal or even better outcomes than conventional therapy.

Methods: We will develop a virtual clinic exergame with 8 types of kinesiotherapy exercises. Afterward, we will conduct a 1:1 randomized clinical trial to compare the practice of kinesiotherapy with exergames (intervention group) against conventional kinesiotherapy (control group). A total of 24 older women will be enrolled for 1-hour sessions performed twice a week, for 6 weeks, totaling 12 sessions. We will assess outcomes using epigenetic blood tests, the Montreal Cognitive Assessment test, the Timed Up and Go test, muscle strength grading in a hydraulic dynamometer, and the Game Experience Questionnaire at various stages.

Results: The project was funded in October 2019. Game development took place in 2020. Patient recruitment and a clinical trial are planned for 2021.

Conclusions: Research on this topic is likely to significantly expand the understanding of kinesiotherapy and the impact of exergames. To the best of our knowledge, this may be one of the first studies exploring epigenetic outcomes of exergaming interventions.

Trial Registration: Brazilian Clinical Trials Registry/Registro Brasileiro de Ensaios Clínicos (ReBEC) RBR-9tdrmw; https://ensaiosclinicos.gov.br/rg/RBR-9tdrmw.

International Registered Report Identifier (IRRID): DERR1-10.2196/32729

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KEYWORDS

elderly women; exergame; epigenome; cognition; kinesiotherapy

Introduction

Background and Rationale

Human aging is a natural process that causes a series of neuropsychomotor changes, such as decreased muscle strength, proprioception, balance, and cognition [1,2]. An option to mitigate this deterioration is kinesiotherapy, a therapeutic exercise that trains body movements and postures in a planned and systemic way, improving the patient's functional capacity, autonomy, and well-being [3].

Neuroprotective effects of physical exercise and the improvement of its clinical and functional outcomes are partly associated with the modulation of epigenetic marks, in both preclinical and clinical studies [4-9]. Epigenetics is the study of heritable changes in gene function that do not entail a change in DNA sequence [10]. Epigenetic marks are modulated by gender and time of the day [11]. Especially for older women, physical exercise has a role in improving health conditions [12-14], which is even indicated in biomarkers [15].

Older people face barriers to take part in exercise, but they identify positive aspects of strength and balance activities [16,17] and report positive perceptions about implementing technology to exercise [18]. Hence, appropriate programs and interventions based on education and training can help overcome the barriers [16]. Likewise, motivation and confidence for older persons can enable better performance in physical exercise [19]. In all these aspects, appropriate interactive technologies can have a facilitating role [20].

Virtual games are beneficial in physical therapy practice, particularly in the rehabilitation of functional balance, postural skills, and motor skills [21-23]. Exergames are virtual games that can capture the user's real movements and promote physical activity, especially for older people [24]. This kind of game encourages the use of body movements to interact with the virtual scenario in a stimulating and integrative way, generating an enriched setting and greater motivation for progressing motor skills [25,26]. Game-based therapy can also be an alternative approach to improve cognitive functions, with improvements in different cognitive domains, such as executive function, visuospatial attention, verbal memory, and working memory [27]. Furthermore, rehabilitation exercises with exergaming have become an option for rehabilitation programs and have been adopted by physical therapists [28].

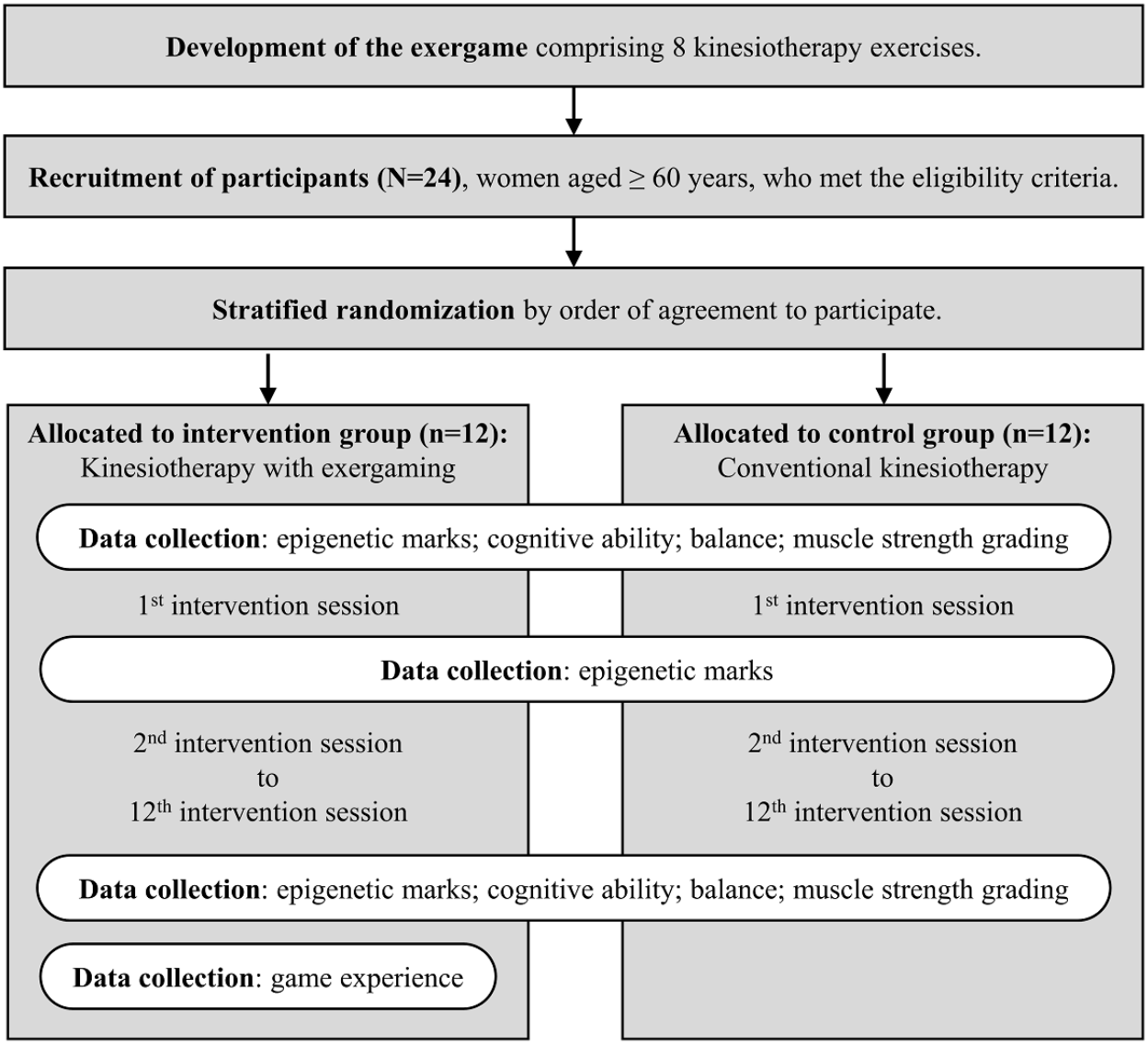
Aims and Hypothesis

There is emerging evidence that physical exercise interventions can alter the epigenome, and the outcomes could be related to specific pathways [29,30]. However, to the best of our knowledge, there is still no evidence in the literature addressing the association of exergaming with epigenetic marks. Given the heterogeneity and complexity of the existing literature, more research is required in this emerging area to identify epigenetic marks that could serve as indicators of exercise adaptations [29]. In this perspective, this study aims to evaluate the effects of kinesiotherapy with exergaming on older women's epigenetic marks and cognitive ability, alongside the evolvement of clinical functional variables. We hypothesize that this kind of therapy can elicit satisfactory results, with similar or even better outcomes than those of conventional therapies.

Methods

This is an applied study with software development and analysis of its effects through a controlled, parallel, two-armed, open-label, randomized clinical trial. Figure 1 shows the procedure flowchart.

Figure 1. Study procedure flowchart.



Exergame Development

Exergames that require an individual to repeatedly reach for an object do not use the full potential of exergaming as a rehabilitation tool [31]. Taking this into account, we will develop an exergame with a virtual scenario based on a physiotherapy clinic. In this environment, 8 types of exercises practiced in kinesiotherapy sessions will be available, including squats, horizontal shoulder abduction, hip abduction, diagonal movement of the upper limb (Kabat diagonals), plantar flexion, elbow extension, elbow flexion, and horizontal shoulder adduction. Reference images from real environments will be used to model the setup and all interactable objects used by the avatars.

The clinic scenario will have windows that show an outdoor view with trees and clouds reacting to the wind. The lighting and animations will also change according to the day and time the user is playing, whether day or night. A male and a female character (avatar) will be available to play, selected according to the gender registered for each user. The objects that the avatar will interact with when performing an exercise will be automatically selected according to the type of exercise. Four camera positions will be implemented in the game. The game will have a menu with options for registration, settings, and types of exercise. During the execution of the exercises, information on the number of repetitions and completed series will appear on the screen, in addition to the execution time.

The exergame will be developed using the programming language C# (Microsoft Corporation), with the game engine Unity 3D (Unity Technologies). Both the scenario and the physiotherapy equipment will be modeled on Blender (Blender Foundation), open-source 3D creation software for animation, simulation, rendering, composition, and motion tracking. The characters will be created in Adobe Fuse (Mixamo), which also offers prebuilt animations and an autorigging tool in the mesh of the created characters. Some other tools, such as Audacity, for editing the sound effects, and Paint.NET (dotPDN LLC) for editing the interface sprites and object textures, may be used in the development of the game.

The participant plays the exergame by watching their avatar on a 42-inch monitor. The motion capture will use an Astra Pro depth sensor (Orbbec 3D Tech Intl Inc) and the software Nuitrack (3DiVi Inc), which analyzes the data obtained by the sensor to identify the user's movements. To identify the completed repetitions and errors, the game will have rigidbody colliders in the avatar and in the scenario, passing the avatar positions to the scripts that evaluate whether the movement was correct or not.

One of the advantages of the proposed exergame over conventional therapy is that the game is more stimulating and has a joyful purpose, which provides a form of biomechanical biofeedback—feedback on measurements of movement, balance, postural control, and force output [32]. The exergame will have a dynamic virtual environment to engage participants, which will include elements such as background music, object sounds, avatars demonstrating movements as a form of instruction, sound and visual effects to reward achievements and exercise conclusions, scores, individual progress history, automatic counting of series and repetitions, the possibility of competition between participants, and control of times and turns. Hence, we expect to enhance the gains achieved during therapy, throughout the sessions, and perhaps even in a shorter period, as achieved by Henrique et al [21].

Sample, Eligibility, and Allocation

We will recruit 24 participants, exclusively women aged 60 years and over, at the School Clinic of Studies and Professional Practices of the Regional Integrated University of Upper Uruguay and Missions, which is located in Erechim, Rio Grande do Sul, Brazil. The sample size was based on the studies that used a similar methodology to assess the effect of exercise on epigenetic marks and the effect of improved functional mobility induced by running in the older women, related to epigenetic marks [8,9], considering the global H4 histone acetylation levels variable from earlier studies [33,34]. Sample size was calculated using G*Power software [35] considering an effect size of 1.3, two tails, an error probability of .05, and a power of 0.8.

After the invitation to take part in the study, the participants will sign a consent form and complete a demographic questionnaire. The following inclusion criteria will be verified: age 60 years or older; ability to ambulate effectively; absence of any reported diagnosis of neurological, cardiac, or any other disease that restricts physical exercise; absence of depression confirmed by the Geriatric Depression Scale—Short Form [36]; cognitive ability confirmed by the Mini-Mental State Examination, Brazilian version [37]; and acceptance of the commitment not to undergo any other physical therapy during the study.

The sample will have stratified randomization for 2 groups with 12 participants each. Patients will be selected by order of agreement to participate in the study until the number of patients stipulated for either of the groups is reached. The intervention group will practice kinesiotherapy exercises with the exergame, whereas the control group will practice conventional kinesiotherapy exercises without exergaming. Owing to the nature of the intervention, masking of the physical therapists and participants is not possible. However, data will be collected and analyzed by professionals masked to the allocation of the groups.

Outcome Measurements

Throughout the clinical trial, we will assess different data for two assays. The first assay will assess the acute and late effects on the participants' epigenetic marks (primary outcome) as well as the cognitive ability (secondary outcome). Meanwhile, the second assay will assess the participants' balance and muscle strength grading (primary outcomes), in addition to the postgame experience (secondary outcome).

First Assay

Epigenetic marks will be assessed with blood tests. The samples will be collected by qualified and verified professionals, from veins located in the antecubital area, in a sanitized and cool place previously prepared for the procedure. Furthermore, 20 mL blood will be drawn using disposable syringes and needles. The venipuncture procedure will be applied and all national biosafety procedures will be followed. Initially, the blood will be divided into two tubes: a tube containing a separating gel that will receive 5 mL blood to obtain the serum. The other tube will contain the EDTA anticoagulant and will receive 15 mL blood. Then, Histopaque will be added in a 1:1 ratio to the tube with EDTA, which will then undergo a series of centrifuges for the extraction of plasma and peripheral blood mononuclear cells. The material will be stored in appropriate containers at −20 °C. Biomarker analysis will be performed using commercially available assay kits, according to the manufacturer's guidelines.

The types of indicators that will be analyzed using biomarkers include plasma levels of the brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family that has an important role in neuroplasticity and is associated with the process of memory and learning. We will also analyze the global acetylation levels of histones H3 and H4, which are epigenetic markers associated with increased transcriptional activity and gene expression. A previous study [9] identified that a single exercise session induced a state of global DNA hypomethylation but did not alter the global acetylation levels of H4 histone. However, these markers were not modified after more sessions, suggesting that epigenetic modulation in response to physical exercise is transient, which justifies an analysis comparing the acute and late effects.

Cognitive ability will be assessed using the Brazilian version of the Montreal Cognitive Assessment protocol [38]. This is a brief screening tool that assesses a wide range of cognitive functions, such as executive functions, visuospatial skills, memory recovery, digits, sentences, abstract reasoning, and orientation. The test time is estimated at 20 minutes and the maximum possible score is 30 points. The cutoff score is 26 points.

Second Assay

The balance will be assessed using the Timed Up and Go test, which determines fall risk and measures, in seconds, the time taken by an individual to stand up from a chair, walk a distance of 3 m, turn, walk back to the chair, and sit down. For healthy

older adults, the ideal time for the test is 10 seconds. When performed between 11 and 20 seconds, it indicates that the individual may have some disability or fragility, which is considered partial independence and low risk of falls. When the test is performed with a time ≥20 seconds, the individual is classified as dependent and has a considerable deficit in physical mobility and a high fall risk [39,40].

Muscle strength grading will be assessed using a push-pull hydraulic dynamometer. This is a device that operates on the principle of traction and compression. An external force is applied to the dynamometer and its spring is tensioned, moving an indicator of the amount of static force applied.

Game experience will be assessed using the postgame module of the Game Experience Questionnaire [41]. It measures players' experience after the gaming session and any aftereffects (eg, returning to reality, fatigue, pride, guilt) using 17 statements with a semantic differential scale response to indicate the level of agreement.

Procedure and Follow-up

During the study, participants in both groups will not be allowed to perform any other type of physical therapy. Intervention sessions for both groups will be carried out twice a week. Each session will last an hour, for 6 weeks, resulting in 12 sessions. This time frame is based on similar studies of Duque et al [42] and Park and Yim [43]. The set of kinesiotherapy exercises was designed based on exercises from successful studies on older rehabilitation [21,44,45], whose movements can be captured by the motion sensor used in the exergame.

We will request all participants to attend sessions wearing dark workout clothes to standardize them and also facilitate body detection by the motion sensor. Each participant will be placed in a room with the setup ready. For the control group, it will be a conventional physiotherapy clinic with the necessary equipment for the exercises. For the intervention group, the environment will contain the same equipment, along with the exergame setup consisting of a 42-inch monitor and the motion sensor.

Both groups will be accompanied by 2 physical therapists throughout the sessions. The professionals will provide instructions and adjust the equipment used in the sessions following a standardized procedure protocol to avoid any type of bias. In the event of an incident (eg, harmful movement, injury, or misuse of equipment), the professional will intervene, pausing the session until the problem is fixed. The session will resume as soon as possible so that the participant can complete the remaining time.

The exercises will use dumbbells, TheraBands, and Swiss ball accessories. The weight of the dumbbells and resistance level of the TheraBand will be proportionally tailored to each participant. We will use the Modified Borg Dyspnea Scale [46] to verify the participant's perception of effort and to define the accessories with an inversely proportional level of difficulty of use. In the first intervention session, for all participants, we will provide a 1-kg dumbbell and a light-resistance TheraBand. Then, at the end of each session, the physical therapists will evaluate each participant's perception of effort in performing the exercises using her respective accessories. This will support the choice of the dumbbell weight and the TheraBand resistance that the participant will use in the following session. Different Swiss balls will be used, depending on the height of the participant: the small version of 55 cm for people with a height of 160–174 cm, and the average version of 65 cm for people with a height of 175–195 cm.

Performed individually, the kinesiotherapy session will start with a warm-up exercise (10 minutes), using a horizontal exercise bike. After that, the following 8 specific exercises will be performed:

1. Squatting with dumbbells in hands, for 3 minutes.
2. Horizontal shoulder abduction with elbows in extension holding the TheraBand and sitting on the Swiss ball, for 3 minutes.
3. Hip abduction with the TheraBand around the lower limbs, for 6 minutes.
4. Kabat diagonals (adapted) with the patient sitting on the Swiss ball, for 6 minutes.
5. Plantar flexion for calf with dumbbells in hands, for 3 minutes.
6. Horizontal shoulder adduction with elbows in extension holding the TheraBand and sitting on the Swiss ball, for 3 minutes.
7. Elbow flexion for biceps using TheraBand and sitting on the Swiss ball, for 3 minutes.
8. Flexion of hamstring, quadriceps, iliopsoas, and gastrocnemius, performed during a series of 30 seconds for each muscle group, repeatedly, for 6 minutes.

After the strength exercises, the participants will perform cervical spine stretching, lateral and posterior trunk stretching, hamstring stretching, and quadriceps, iliopsoas, and gastrocnemius exercises. The exercises will be performed in a series of 30 seconds, resulting in 10 minutes of activities. Among the different types of exercises, there will be intervals of at least 30 seconds for rest and adjustment of game settings.

The intervention group will perform the same procedure and use the same kinesiotherapy equipment as the control group but playing the exergame with its 8 specific exercises as the basis of the session. The exercises will always be performed in the same order and duration, from the first to the last session. During the intervention, there will be a tolerance of only 2 absences per participant, which must be recovered immediately in the same week of the absence. Otherwise, the participant will be removed from the study.

Data Collection

Blood test values to assess epigenetic marks will be collected from all participants at three stages: at baseline; after the first session of the intervention, to verify the acute effects; and after the complete intervention, to verify the late effects. Cognitive ability, balance, and muscle strength values will also be collected from all participants at two stages: at baseline and after the complete intervention. Game experience data will be collected exclusively from the participants who played the game (intervention group) after the intervention is completed.

Statistical Analysis

Basic quantitative data will be determined by mean, SD, and median. Categorical data will be determined by simple frequency. Numeric data will be analyzed using statistical software SPSS, version 22 (IBM Corporation). The normality of the data will be tested using the Shapiro-Wilk test. Moreover, depending on the distribution, we will use one-way factor analysis of variance with Tukey post hoc (parametric data), or Kruskal-Wallis test (nonparametric data). To evaluate the main outcomes of the study, a generalized estimation equation with gamma distribution will be performed. To correlate the data, we will apply Spearman and Pearson analyses considering a 95% CI (P<.05). All analysis techniques can be adjusted or modified, if required, by the characteristics of the collected data.

Results

The project was funded in October 2019. Game development took place in 2020. Patient recruitment and clinical trial are planned for 2021.

Discussion

The therapeutic resources used in physiotherapy, including the use of virtual reality technologies applied to kinesiotherapy, have been highlighted in recent years. Moreover, physical therapy has used technology to make interventions more engaging, convenient, and fun. Among the many possibilities offered by technology, exergames can be a powerful tool, with opportunities for users to participate in different rewarding experiences, as they rely on motivational aspects [25] and have adaptive strategies to each user, regardless of their motor and cognitive skills [47]. Exergames are a safe, feasible, and beneficial tool for physical exercises by older people [48]. They can combine physical activity, game dynamics, challenges, and achievements in a comfortable environment, merging real-world elements and virtual contents in a single view [48,49]. O'Loughlin et al [50] stated that exergaming is a healthier alternative to sedentary behavior, due to higher energy expenditure and improved physical fitness. In addition, exergames may improve balance, motor coordination, and muscle strength, increasing adherence to exercise in the older population while keeping them physically and socially motivated [25,51-53].

Technological solutions are flexible and have the potential to be accessible, reaching more users at the same time [54]. They also introduce a new style of rehabilitation and practice of physical activities, allowing health professionals to remotely assess the progress of patients and adjust the training strategy accordingly, offering customized experiences related to each user profile, while motivating patients by engaging family members, caregivers, and friends [55,56]. However, a considerable part of the exergames used in physiotherapy is derived from commercial sources [52,57-60], generally not designed exclusively for the older population, or are not based on specific therapy protocols [61]. Moreover, new studies should include games that can target multiple physical functions to determine the extent to which exergaming can contribute to keeping older adults active and healthy [31]. Therefore, it is plausible that an exergame developed from a specific kinesiotherapy model designed exclusively for the older population can elicit better outcomes, which justifies the exergame that we will develop.

We expect that both groups have improvements in muscle strength, balance, and cognitive ability, as both of them will exercise. However, due to the motivational and enriching aspects of the exergame, we expect the intervention group to show a significant improvement compared to the control group. We assume that improvement in functional clinical outcomes in the exergame group will be associated with increased BDNF levels and global acetylation of histones H3 and H4. Strategies that modulate BDNF and acetylation levels might be indicated to improve memory in the older population. Many studies have already shown that exercise is a strong epigenetic modulator that increases BDNF levels [7-9,33,62].

Research on this topic is likely to significantly expand the understanding of kinesiotherapy and the impact of exergames for older women. To the best of our knowledge, this may be one of the first studies exploring epigenetic outcomes of exergaming interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the grant agency.
[PDF File (Adobe PDF File), 511 KB - resprot_v10i10e32729_app1.pdf]

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Abbreviations

BDNF: brain-derived neurotrophic factor
FAPERGS: Research Foundation of the State of Rio Grande do Sul

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Protocol

Noisy Galvanic Vestibular Stimulation Combined With a Multisensory Balance Program in Older Adults With Moderate to High Fall Risk: Protocol for a Feasibility Study for a Randomized Controlled Trial

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Abstract

Background: Reduced mobility and falls are common among older adults. Balance retraining programs are effective in reducing falls and in improving balance and mobility. Noisy galvanic vestibular stimulation is a low-level electrical stimulation used to reduce the threshold for the firing of vestibular neurons via a mechanism of stochastic resonance.

Objective: This study aims to determine the feasibility of using noisy galvanic vestibular stimulation to augment a balance training program for older adults at risk of falls. We hypothesize that noisy galvanic vestibular stimulation will enhance the effects of balance retraining in older adults at risk of falls

Methods: In this 3-armed randomized controlled trial, community dwelling older adults at risk of falling will be randomly assigned to a noisy galvanic vestibular stimulation plus balance program (noisy galvanic vestibular stimulation group), sham plus balance program (sham group), or a no treatment group (control). Participants will attend the exercise group twice a week for 8 weeks with assessment of balance and gait pretreatment, posttreatment, and at 3 months postintervention. Primary outcome measures include postural sway, measured by center of pressure velocity, area and root mean square, and gait parameters such as speed, step width, step variability, and double support time. Spatial memory will also be measured using the triangle completion task and the 4 Mountains Test.

Results: Recruitment began in November 2020. Data collection and analysis are expected to be completed by December 2022.

Conclusions: This study will evaluate the feasibility of using noisy galvanic vestibular stimulation alongside balance retraining in older adults at risk of falls and will inform the design of a fully powered randomized controlled trial.

Trial Registration: New Zealand Clinical Trials Registry (ACTRN12620001172998); https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379944

International Registered Report Identifier (IRRID): DERR1-10.2196/32085

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KEYWORDS

older adult; balance; rehabilitation; noisy galvanic vestibular stimulation; nGVS; brain stimulation

Introduction

Background

The contribution of age-related decline in postural responses to reduced mobility and falls in older adults is well established [1-4]. The mechanisms underlying this deterioration are complex but are thought to include impaired function and processing of sensory information from the visual, vestibular, and somatosensory systems. The vestibular system is perhaps the least understood of these balance systems. However, rich connections between the hippocampus, cerebellum, and brainstem suggest that treatments designed to enhance the vestibular system have the potential to improve postural stability and balance [5-8].

Noisy galvanic vestibular stimulation is a subsensory galvanic stimulation delivered with a superimposed Gaussian noise signal. The proposed mechanism of action is based on the principle of "stochastic resonance," in which noisy galvanic vestibular stimulation enhances weak sensory input signals from the vestibular apparatus [9,10]. This then enhances vestibular perception and vestibulospinal reflex function, both essential components of the sensory feedback loop for balance [11-13].

All sensory systems decline with age [14]; however, there is strong evidence that balance training can reduce the risk of falls in older adults and improve clinical tests of stability [15-17]. Although there are known benefits of rehabilitation programs for balance retraining, less is known about the effect of noisy galvanic vestibular stimulation on postural control [18,19]. Emergent research in humans suggests immediate benefits to static balance. Inukai et al [20] reported immediate improvements in standing balance when noisy galvanic vestibular stimulation was administered to healthy older adults, and Iwasaki et al [4] demonstrated a similar positive effect in patients with bilateral vestibular dysfunction. There is some evidence that this benefit may be sustained. Fujimoto et al [21] examined the effect of 30 minutes of noisy galvanic vestibular stimulation on balance and found that a positive effect was maintained for up to 3 hours after exposure to the intervention. These improvements were further enhanced by a subsequent 30-minute exposure, which also sustained the beneficial effects. However, this sustained effect has not been replicated consistently in other studies; Inukai et al [22] found a poststimulation effect in contrast to Nooristani et al [23] and Keywan et al [24] who did not. A secondary analysis by Fujimoto et al [21] discovered that noisy galvanic vestibular stimulation resulted in significantly greater improvements in participants who were more unsteady on initial assessment [25]. This suggests that either noisy galvanic vestibular stimulation has a greater effect on the hypofunctional vestibular system or that different noisy galvanic vestibular stimulation parameters and experimental designs play a role in these findings. Noisy galvanic vestibular stimulation has also shown positive effects on walking balance, with Wuehr et al [12] and Iwasaki et al [26] finding that noisy galvanic vestibular stimulation resulted in an immediate positive effect on gait and in adults with bilateral vestibular pathology. However, to date, there are no studies of noisy galvanic vestibular stimulation in older adults who present with a fall risk, and no studies have investigated the repeated application of noisy galvanic vestibular stimulation as a clinical intervention. No study has investigated the augmented effect of concurrent noisy galvanic vestibular stimulation and balance rehabilitation to improve stability. We plan to redress these limitations by examining the impact of a balance rehabilitation program augmented with noisy galvanic vestibular stimulation in older adults at risk of falls.

Objectives

This study aims to assess the feasibility of a future definitive randomized trial examining the effect of balance rehabilitation augmented with noisy galvanic vestibular stimulation in older adults at risk of falls. The primary objective is to assess the feasibility of the study process, including (1) rate of participant recruitment, conversion, and retention; (2) feasibility of screening processes; (3) utility of data collection and outcome measures; and (4) acceptability and suitability of the intervention and study procedures.

Our secondary objectives are to (1) evaluate participant opinions of the intervention as a basis for refinement of the definitive trial; (2) select a responsive and meaningful outcome measure; and (3) to inform the power and sample size calculations for the future full randomized controlled trial.

Methods

Trial Design

This study is a 3-armed randomized controlled trial design with a qualitative component. A total of 72 participants will be randomly allocated in a 1:1:1 ratio to a noisy galvanic vestibular stimulation group, sham group, or no intervention control group. Recruitment will close once 24 participants have been recruited into the noisy galvanic vestibular stimulation arm. Outcome assessment will occur at baseline (week 1), posttreatment (week 10) and at the 3-month follow-up posttreatment (Table 1).

Table 1. Standard Protocol Items-Recommendations for Interventional Trials tabulation of study enrollment, interventions, and assessments.

Study events	Study period					
	Enrollment	Postallocation				Closeout
		Week 1	Week 2-9	Week 10	Week 22	
Eligibility screen						
STEADI[a] questions	✓					
Three-step command	✓					
Demographics (age, sex, and ethnicity)	✓					
Exclusion screen for nGVS[b]	✓					
Informed consent	✓					
Written informed consent		✓				
Allocation	✓					
Assessments						
Montreal Cognitive Assessment		✓				
Activities-specific balance confidence		✓		✓	✓	
Center of pressure		✓		✓	✓	
Single and dual task gait		✓		✓	✓	
Timed Up and Go		✓		✓	✓	
Four-Stage Balance Test		✓		✓	✓	
Functional Gait Assessment		✓		✓	✓	
30-second chair stand test		✓		✓	✓	
Triangle completion task		✓		✓	✓	
4 Mountains Test		✓		✓	✓	
Adverse event monitoring			✓			
Intervention fidelity monitoring			✓			
Semistructured interviews				✓		
Intervention						
Exercise+nGVS			✓			
Exercise+sham nGVS			✓			
Exercise (control)						✓

[a]STEADI: Stop elderly accidents, deaths, and injuries.

[b]nGVS: noisy galvanic vestibular stimulation.

Semistructured interviews posttreatment will investigate the acceptability of the research processes and the intervention from the perspectives of study participants and physiotherapists.

Participant Recruitment and Eligibility Criteria

Recruitment

Older adults will be recruited from the community in a staged manner to determine the feasibility of recruitment methods. Suitable candidates will be approached via newspaper advertisements, local medical practices, newsletters targeting older adult community groups, retirement villages, social media, community notice boards, presentations to local groups, and professional networks. Data will be collected on the efficacy of each method in terms of response rate, proportion of respondents who were eligible, eligible respondents who subsequently consented to the study, and the number of participants who completed the study.

Screening

People interested in participating will contact a member of the research team via telephone or email. Initial screening and eligibility will be assessed by a trained research assistant via telephone and data entered into the REDCap database. Eligible participants who provide consent will be enrolled into the study.

Inclusion Criteria

Participants are eligible for inclusion if they meet the following criteria: (1) aged ≥65 years or Maori or Pasifika aged ≥55 years, (2) independently living in the community, (3) considered at risk of falls based on the stop elderly accidents, deaths and

injuries (STEADI) fall screening questions (Textbox 1) [27], and (4) able to stand independently for 5 minutes and ambulate for 10 m with or without a walking aid.

Textbox 1. Stop elderly accidents, deaths and injuries (STEADI) fall risk screening questions.

Screening questions (answering yes to any of these questions indicates a fall risk)

- Have you fallen in the past year?
- Do you feel unsteady when standing or walking?
- Do you worry about falling?

Exclusion Criteria

Participants will be excluded if any of the following criteria are present: (1) diagnosis of a neurological condition, (2) pacemaker, (3) metal implants in the head or neck, (4) vertigo, (5) current diagnosis of migraine, and (6) cognitive impairment to the extent that they are unable to follow a 3-step command on the telephone.

Randomization

Participant group allocation will be by stratified random computer generation using a "minimization" algorithm in MinimPy (Msaghaei) to stratify groups by age, sex, and fall history in the past 6 months [28-30]. Allocation will be concealed in an opaque envelope identified only by the identification number of the participant and given to the participant after the initial assessment. Participants will be requested to open the envelope only after exiting the testing room. A contact number will be included in the envelope if participants wish to discuss their allocation.

Blinding

The noisy galvanic vestibular stimulation and sham group participants, assessors, therapists, and data analysts will be blinded to the group allocation. Measures will be taken to minimize the potential for the assessor and treating therapist to become unblinded. This will include avoiding discussions about the participants in front of the assessor and treating therapist. When participants are contacted to make appointments for the assessment, the team members involved will use this opportunity to remind participants not to reveal details of any treatment they have received to the assessor. A register of the unblinding events will be maintained.

Assessment

Outcome measures will be collected by a single investigator who will be blinded to the allocation and not involved in any aspect of the intervention.

Data Collection Methods

Once participants are recruited to the study and have given consent, they will attend three assessments at baseline, posttreatment, and at the 3-month follow-up (Table 1). Assessors will be trained in a protocol by a member of the research team who is familiar with the testing procedures. Assessments will be audited for quality and data completeness and checked for precision by the project manager once 10% of the data has been collected. A summary of the checks will be provided to the data monitoring committee. Any reports of adverse events will be reported and discussed at the monthly steering committee meeting.

Outcomes

Participant Characteristics

The participant population will be described using demographic data, anthropometric data, including weight and height, the Montreal Cognitive Assessment, a brief cognitive screening tool [31], and the Activities Balance Confidence Scale, a structured questionnaire measuring an individual's confidence performing specific activities [31].

Postural Sway Parameters

Postural sway will be calculated from center of pressure (COP) excursions on a force plate [4] (AMTI) in eyes open and eyes closed conditions. COP values of velocity, area, and root mean square during static standing have been shown to be precise, quickly administered assessments [32,33], with minimal ceiling and floor effects [34,35], and excellent sensitivity in the identification of older adult fallers [36-38]. In addition, we will investigate the relationship between the COP excursion and velocity and acceleration profiles of the head.

Gait and Mobility Performance–Based Measures

Performance-based measures of balance, gait, and leg muscle strength will indicate change in function and postural control. These tests are widely used in research for older adults with and without pathology, and all have norm-referenced values and robust clinimetric properties.

Gait will be measured using a 7 m long × 0.6 m–wide instrumented walkway, GAITrite, gold software version 3.2b, (CIR systems), in both single and dual task conditions [39]. Spatiotemporal parameters of interest include step velocity, length, width, double support time, and variability [40,41]. In addition, we will investigate the relationship between these spatiotemporal measures and the velocity and acceleration profiles of the head. A 9-camera motion capture system sampled at 200 Hz will record 3D kinematic data during the balance and gait measures. The 3D kinematic data will be exported to MATLAB (MathWorks, Inc) where a 6 degrees of freedom model will be constructed from shoulder and head marker position data. The model will consist of two triangles in 3D space, the first one corresponding to the shoulders and the second one for the head. The time series for the roll, pitch, and yaw angles of the head will be calculated with respect to the shoulders. Linear displacement across the mediolateral and anterior-posterior axes and the angular displacement about the

vertical axis will be computed from these time series for a quantitative analysis of the head movement.

A range of mobility performance measures will be used. The Functional Gait Assessment assesses balance during walking under different conditions (speed change, head turn, pivot turn, obstacle clearance, and narrow base) [42,43]. The 30-second chair stand test measures functional leg strength. Participants will be asked to stand up from a chair and sit back down as often as they can within 30 seconds [44]. The Timed Up and Go test is a simple test used to assess the mobility of a person and requires both static and dynamic balance. It involves timing a person rising from a chair, walking 3 m, turning around, walking back to the chair, and sitting down. The Timed Up and Go test is considered a valid, reliable, and sensitive measure of mobility and balance in older adults [45,46]. For the Four-Stage Balance Test, participants are asked to stand in 4 progressively more challenging positions for 10 seconds with their eyes open and without using an assistive device. If the patient can hold a position for 10 seconds without moving their feet or needing support, they go on to the next position. Otherwise, the test is stopped. An older adult who cannot hold the tandem stance for 10 seconds is considered at increased risk of falling [47].

Spatial Memory

Spatial memory is strongly influenced by vestibular inputs [35,48] and will be assessed using the triangle completion task and the 4 Mountains Test. The triangle completion task combines vestibular and somatosensory inputs and interacts with cognitive and motor processes to perceive self-motion and generate a cognitive map of space [49-51]. The 4 Mountains Test uses a delayed match-to-sample paradigm on a computer-based image [52]. This is a highly sensitive test in older adults with mild cognitive impairment and can be easily applied in routine clinical practice [53].

Qualitative Assessment

A qualitative assessment in the form of a semistructured interview designed to investigate the acceptability of the treatment will occur at week 10 for selected noisy galvanic vestibular stimulation and sham participants. We aim to interview 5-6 participants in the noisy galvanic vestibular stimulation intervention group with a sample purposively selected to represent variation in intervention compliance and response; 2 sham participants will also be interviewed to explore the acceptability of the trial process. Physiotherapists delivering the intervention will be interviewed to explore the study processes, acceptability, and value of the intervention from their perspective. Semistructured interviews will be transcribed verbatim and uploaded to NVivo. We will conduct thematic analysis of the data using the 6-stage process of analysis (transcription, reading and familiarization, coding, searching for themes, reviewing themes, defining and naming themes, and finalizing the analysis) by Braun and Clarke [54]. Data will be initially analyzed at a semantic level to draw on the reflections of participants in relation to processes and practical aspects of the assessments and interventions. However, researchers will also identify latent themes, such as underlying ideas and assumptions, which are theorized to shape and inform semantic data.

Intervention

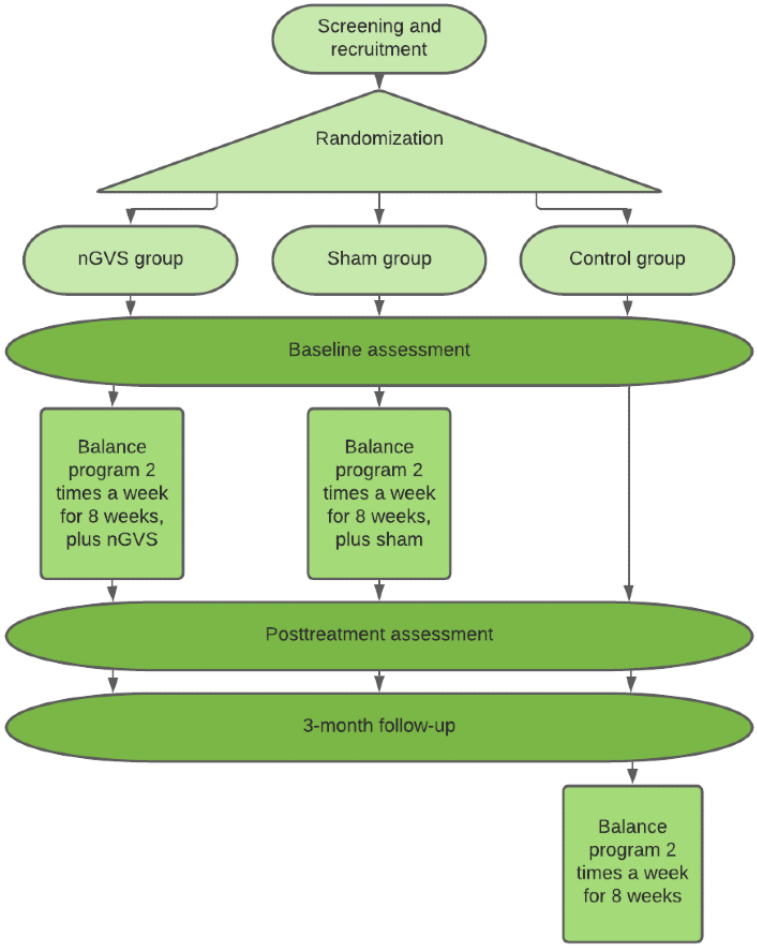
The balance retraining program focuses on exercises and activities that stimulate the vestibular system and the integration of all sensory inputs for effective postural control (Table 2) [7,45,47]. The exercises are delivered in a group setting of up to 6 participants with difficulty in the exercises being individualized for each participant. The balance retraining program is delivered by an experienced and registered physiotherapist with 1 assistant for groups of 4 and above. Participants in the noisy galvanic vestibular stimulation group will receive 30 minutes of white noise galvanic vestibular stimulation during the exercise program; the sham group will receive sham stimulation during the exercise program, and the control group will receive no intervention [4,21]. The noisy galvanic vestibular stimulation generates a 0 mean random signal with equal intensities at different frequencies via electrodes applied over the mastoid process, which are attached to a noisy galvanic vestibular stimulation device (Galvanic Stimulator 0811, Soterix Medical). The intensity is set at 0.5 mA and is of imperceptible magnitude.

The noisy galvanic vestibular stimulation and sham groups will commence the exercise program within 10 days of the initial assessment. The exercise group will be offered to the control group after the 3-month follow-up assessment at the end of their participation in the study (Figure 1).

Table 2. Summary of the multisensory balance program.

Category	Time (minutes)	Examples of exercises
Warmup	5	Multidirectional walking, turning, changing speed and size of movement
Vestibular	10	Standing, head turns with a target- fixed- gaze stimulating the vestibular ocular reflex. Standing on unstable surfaces eyes closed
Vision	5	Eyes open walking on narrow beam and standing on unstable surfaces
Somatosensory	5	Testing individuals' limits of stability; multidirectional lean, standing on unstable surfaces
Mobility-center of gravity control	5	Walking a straight line, weaving and turning during gait, changing base of support and posture simultaneously while moving from low to high surfaces
Aerobic	5	Exercycle

Figure 1. Participant flow through the study. nGVS: noisy galvanic vestibular stimulation.



Data Management

Data will be entered directly into customized REDCap digital data collection forms; any paper forms will be uploaded into the REDCap data management system. REDCap access is password-protected and requires dual identification for entry. Forms will have internal checks for completeness and where appropriate individual criteria will have automatic range checks. All data will be deidentified on exportation from the database with analyses performed by a blinded member of the research team. Blinding will not be lifted until data collection and final follow-up assessment has been completed. Data will only be accessible to the research team. The results will be made available to participants on request and will be published in a peer-reviewed journal.

Statistical Methods

The analysis will focus on univariate models, such as linear mixed models, but include measures of association. An examination of within-subject data will be carried out to measure changes in key outcomes. This will help refine participant selection, protocol, and suitability of outcome measures for the full study. Responsiveness metrics such as effect size and standardized response mean will be calculated for postural control outcomes to inform the selection of the primary outcome and power calculations for the intervention study.

Semistructured interviews will be transcribed verbatim and uploaded to NVivo. Data will undergo thematic analysis using the Braun and Clark six-stage process of analysis (transcription, reading and familiarization, coding, searching for themes, reviewing themes, defining and naming themes, and finalizing the analysis) [54]. Data will be initially analyzed at a semantic level to draw on the reflections of participants in relation to processes and practical aspects of the assessments and interventions. However, researchers will also aim to identify latent themes—the underlying ideas and assumptions that are theorized to shape and inform semantic data.

Threats to Attainment of Study Goals

Overview

As a feasibility study investigating a novel treatment, there are a number of aspects of the study that could impact both the attainment of study goals and progression to a fully powered study. Possible threats identified by the study team are the inability to recruit, poor tolerance for noisy galvanic vestibular stimulation, technical issues with noisy galvanic vestibular stimulation, and adverse reactions to noisy galvanic vestibular stimulation. Although there have been very low rates of adverse effects with noisy galvanic vestibular stimulation, the participants in this study receive a larger cumulative dose of noisy galvanic vestibular stimulation compared with previous studies.

The trial will be deemed a success based on the following: (1) recruitment at a rate of 2 participants per week; (2) participants attending 75% of available exercise sessions over 8 weeks; (3) achieving 80% data completeness at each time point; (4) report of no serious adverse events related to the intervention; and (5) a subjective sense of perceived benefit, enjoyment, and engagement in the program present in participants who underwent qualitative assessment.

On the basis of previous research, we estimate that a sample of 72 would be sufficient to investigate feasibility and to determine the sensitivity of our outcome measures to inform sample size calculation for the full study.

Monitoring

The project manager will manage the day-to-day running of the study. Before study commencement, training sessions for clinical and research staff will be conducted. Fidelity will be ensured by the procedures outlined in Table 3. The data monitoring committee will consist of the research team, DT, SL, PFS, YW, and RM, who will meet monthly via Zoom. They will monitor the study to meet fidelity goals, adverse events, and unintended effects. Adverse events will be recorded on an incident form by the team member concerned, and the project manager and principal investigator will be informed by email or phone as appropriate. They will choose a course of action according to the study protocol and inform all relevant members of the research team. Compensation to those who are harmed during the trial is available to participants via the Accident Compensation Corporation, pending an eligible claim. It will be the responsibility of the principal investigator in discussion with the data monitoring committee to make the final decision to terminate the trial.

Table 3. Intervention fidelity.

Program component	Definition	Success criteria
Staff training		
Training	• Protocols are standardized and training involves didactic teaching, role playing and modeling	• Protocol read and training modules completed by all treating physiotherapists
Supervision	• Frequency and duration of supervision are set out	• Therapists are supervised in their initial treatment sessions and then have "spot checks" for compliance with the exercise program, progressions and documentation. All therapists have a contact number of the PI[a] and project manager in the case of an adverse event or self-identified queries or supervision requirements
Measurements	• Establishing compliance with delivery of treatment	• Treatments recorded on a customized, standardized form. Checked by the project manager to ensure data completeness
Recruitment		
Methods	• Staged approach to advertising	• Data collected regarding methods of recruitment and number of people who responded via each method, response rate, number of responders sent a participant information sheet after initial contact
Eligibility	• Number of responders who were eligible and consented to the study. Reasons for ineligibility or deciding not to consent	• Screening data recorded on a standardized form • Average recruitment over the study of 2 participants per week
Intervention delivery		
Intervention differences	• Dose of exercise and noisy galvanic vestibular stimulation intervention	• Expected dose and core components of the program as per the intervention protocol were recorded on the standardized program record
Therapist competence	• Experience and competence	• Years of experience and areas of practice recorded for all treating therapists
Monitoring drift	• Ensure program delivered correctly throughout the program	• Physiotherapists completed and returned a standardized record of all treatment visits. One visit per program between week 6 and 8 by a PI or project manager to ensure program continues to be delivered correctly
Corrective feedback	• Feedback procedures in place	• Ongoing support and mentoring available if discrepancies noted during monitoring of treatment programs and documentation
Intervention receipt		
Dose received	• Data collected regarding the number of sessions attended for each participant • If a participant does not attend, they are followed up with a phone call to assess any barriers to attendance • Petrol vouchers will be given to defray travel expenses	• Goal of 75% exercise sessions attended over 8 weeks
Participant understanding	• Qualitative interview	• A subjective sense of perceived benefit, enjoyment, and engagement in the program present in participants who underwent qualitative assessment

Program component	Definition	Success criteria
Participant adherence	• Data collected regarding completion of follow-up data collection sessions. Participants may be contacted by phone, email and mail depending on their preference and every effort will be made to provide a mutually convenient time for the assessment • Petrol vouchers will be given to defray travel expenses	• Checks for data completeness, 95% of data present at each time point

[a]PI: principal investigator.

Ethical Considerations

Ethics approval has been obtained from the Health and Disability Ethics Council New Zealand (20/STH/111), with the approval of the Auckland University of Technology Ethics Committee (20/310). The trial has been prospectively registered with the Australia New Zealand Clinical Trials Registry (ACTRN12620001172998) and has a Universal Trial Number of U1111-1241-2231.

Any amendments to the protocol will be done with approval from the Health and Disability Ethics Council, and the locality will also be informed (via the Auckland University of Technology Ethics Committee).

Results

Recruitment for our pilot study began on November 26, 2020 the protocol version is 3.0 July 2, 2021. Initial recruitment was slow due to the COVID-19 pandemic, and some exercise groups were affected due to short periods of restrictions on gatherings affecting our region. However, despite these challenges, data collection and analysis will be completed by December 2022.

Discussion

This study aims to deliver novel findings relevant to older adults at risk of falls. This study is the first step toward determining whether noisy galvanic vestibular stimulation can effectively and safely enhance balance and stability in a balance retraining program. Preliminary evidence suggests that the use of subsensory noisy galvanic vestibular stimulation to enhance vestibular signals to the brain also improves stability during quiet standing and gait [4,20,21,25,26]. This study will assess the feasibility of administering a balance retraining program augmented by noisy galvanic vestibular stimulation for older adults at risk for falls. The results of this study will inform the design of a future definitive randomized controlled trial.

Designing a trial to be conducted in a community setting presents challenges. Although community exercise programs are popular among older adults, older adults at risk of falling are a more vulnerable group who may have less access to the community or have anxiety about their stability and therefore be less represented in these groups. There has also been a public health push worldwide for older adults to *stay home and stay safe* during the ongoing COVID-19 outbreak. This has potentially led to physical barriers to community involvement, as well as mental and emotional barriers to commitments outside the home.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports from the Health Research Council of New Zealand.
[PDF File (Adobe PDF File), 595 KB - resprot_v10i10e32085_app1.pdf]

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Abbreviations

COP: center of pressure
STEADI: stopping elderly accidents, deaths and injuries

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Protocol

A Guided Internet-Based Problem-Solving Intervention Delivered Through Smartphones for Secondary School Pupils During the COVID-19 Pandemic in India: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: "POD Adventures" is a gamified mental health intervention delivered via a smartphone app and supported by counsellors for a target population of secondary school students in India. This paper describes the protocol for a pilot randomized controlled trial of a remotely delivered version of the intervention in the context of COVID-19 restrictions.

Objective: Our objectives are to assess the feasibility of research procedures and intervention delivery and to generate preliminary estimates of the effectiveness of the intervention to inform the sample size calculation of a full-scale trial.

Methods: We will conduct a parallel, 2-arm, individually randomized pilot controlled trial in 11 secondary schools in Goa, India. This pilot trial aims to recruit 70 participants with a felt need for psychological support. Participants will receive either the POD Adventures intervention delivered over 4 weeks or usual care comprising information about local mental health services and national helplines. Outcomes will be assessed at two timepoints: baseline and 6 weeks post randomization.

Results: The first participant was enrolled on January 28, 2021, and 6-week assessment completed on April 4, 2021. Owing to a second wave of the COVID-19 pandemic in India, schools in Goa were closed on April 22, 2021. Trial participants are currently receiving the intervention or completing follow-up assessments.

Conclusions: This pilot trial will help understand the feasibility of implementing and evaluating a remotely delivered digital mental health intervention in a low-resource setting. Our findings will be used to design future trials that can address difficulties of accessing psychosocial support in-person and support wider efforts to scale up evidence-based mental health interventions for young people.

Trial Registration: ClinicalTrials.gov NCT04672486; https://clinicaltrials.gov/ct2/show/NCT04672486

International Registered Report Identifier (IRRID): DERR1-10.2196/30339

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KEYWORDS

randomized controlled trial; internet-based intervention; smartphone; adolescent; schools; mental health; COVID-19; app; protocol; problem-solving; intervention; teenager; young adult; India; feasibility; effective

Introduction

Globally, 10%-20% of adolescents experience mental health conditions, but the majority of them do not seek help or receive care [1,2]. The COVID-19 pandemic has increased the incidence of some mental disorders among the youth and has exacerbated existing mental health problems [3-7], with worsening mental health outcomes linked to social isolation, disrupted education, and worries about the future [8].

The pandemic has also led to rapid and large-scale changes in service provision, particularly in the transition to internet-based delivery of care [9,10]. Simultaneously, reviews of digital mental health interventions consistently raise concerns about the accessibility of digital technologies among disadvantaged groups [11] and difficulties keeping users engaged even among groups with access to technology [12]. Though promising gamified approaches have recently emerged [12,13], evidence from low-resource settings is especially scare [14,15].

The current protocol describes a pilot feasibility trial of "POD Adventures"—a novel gamified intervention delivered via a smartphone app and supported remotely by counsellors for a target population of secondary school students in India. Although the intervention was developed prior to the COVID-19 pandemic, the timing of the COVID-19 outbreak meant that the trial was launched in the midst of lockdowns and extended school closures. This required a pragmatic trial design that examined feasibility parameters related to the remote delivery and evaluation of POD adventures specifically, as well as offering insights into more general issues related to optimizing recruitment and sustaining engagement in internet-based trials and interventions.

POD Adventures is part of the PRIDE research program (2016-2022), which was conceived to address the scarcity of evidence-based interventions for common adolescent mental health problems in India and low-resource settings more broadly. This has involved the development and evaluation of a suite of transdiagnostic psychological interventions that can be delivered by nonspecialist ("lay") counsellors in under-resourced school settings [16-18]. POD Adventures was conceptualized as an open-access, early intervention to promote adaptive coping and mitigate risks for developing more severe and socially disabling mental health problems in the longer term. The app was collaboratively designed with adolescents by using a person-centered approach [19]. The intervention integrates brief guidance from a lay counsellor with self-guided digital content from an app, in line with findings that human facilitation can enhance engagement with and outcomes of digital mental health interventions [12,20]. Co-design workshops with young people and iterative piloting suggested that the optimal delivery mode for POD Adventures involved small group sessions with up to 6 students working independently on smartphones under the supervision of a counsellor. This offline, school-based format was evaluated in 2019-2020 as part of an uncontrolled cohort study (N=248), with findings suggesting that the intervention was acceptable, engaging, and feasible to deliver in school settings [18].

This paper describes the protocol for a pilot randomized controlled trial on POD Adventures delivered in an alternative internet-based format, necessitated by COVID-19–related school closures in 2020-2021. School disruptions led us to reposition the intervention on the internet and remotely delivered for students to use at home. The intervention maintains all elements of the pre-existing digital specification, although modifications have been made for internet-based recruitment and remotely delivered guidance from counsellors (Multimedia Appendix 1). The specific objectives of this trial are to assess the feasibility of research procedures and intervention delivery and generate preliminary estimates of the effectiveness of the intervention to inform the sample size calculation for a full-scale trial.

Methods

Design

This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines [21]. The study uses a parallel, 2-arm, individually randomized pilot controlled trial design. Outcomes will be assessed at two timepoints: baseline and 6 weeks post randomization.

Setting

The trial will be conducted in partnership with 11 coeducational, government-aided, English-medium secondary schools in Goa, India, with an overall sampling frame of approximately 2500 students. Schools are relatively small with an average of 230 students within grades 9-12, which will be targeted in this study. Goa is one of India's most urbanized states and offers a relevant context in which to evaluate a technology-enabled intervention intended for low-resource settings. The schools comprise adolescents from both centrally located urban and remote rural areas of the state.

Eligibility Criteria

Eligible participants will (1) be enrolled in grades 9-12 (ages 13-19 years) in collaborating schools, (2) have access to an internet-enabled Android smartphone with a valid phone number for the duration of the pilot trial, (3) be able to read and understand English, and (4) provide their assent and parental consent (for participants aged <18 years).

We will exclude students who (1) are unable to understand intervention material (eg, owing to a reading or hearing disability or inability to comprehend English) and (2) are identified as having an elevated risk of self-harm or suicide and requiring external referral, based on a brief screening questionnaire and follow-up structured interview.

Interventions

Intervention Arm

Content

POD Adventures is grounded in the stress-coping theory [22], with a mechanistic focus on problem-solving. The content of the POD Adventures app comprises two sections: "Adventures," which teaches problem-solving concepts and methods through contextually appropriate games; and "My POD," which scaffolds the student through the application of step-by-step problem-solving procedures to their own prioritized problems. This is built around the acronym "POD," which corresponds to three problem-solving steps: (1) identify 1 or more current distressing or impairing problems ("Problem identification"), (2) identify ways of modifying the chosen problem or the accompanying emotional response and select the most promising option ("Option generation"), and (3) implement the chosen solution and evaluate the outcome ("Do it") (Table 1). These problem-solving steps were originally refined and evaluated for use in nondigital intervention formats through earlier PRIDE studies [16]. The app will be provided in English with Konkani or Hindi (local language) voice-over options.

Table 1. Intervention overview.

Content sections	Description	Delivery
Problem identification	Problem identification and prioritization. This section includes practicing an emotion regulation exercise of "colour breathing," a guided breathing exercise with visualization.	Individual telephone onboarding to orient the student to the app and build rapport. Independent gameplay of the app with support and troubleshooting as required.
Option generation	Generating options to solve the identified problems, learning to weigh pros and cons, and selecting the best option. This section includes practicing mindful stretching.	Independent gameplay of the app with support and troubleshooting as required.
"Do it" plan	Making a "do it" plan for selected option(s); practicing an emotion regulation exercise of "happy place"—guided imagery exercise of imagining a place the participant feels happy, safe, and calm.	Independent gameplay of the app with support and troubleshooting as required.
Review	Reviewing the outcomes of the "do it" plan and making a revised plan where necessary; practicing any emotion regulation exercise of the participant's choice.	Individual telephone review of student's progress and understanding of POD steps. Independent gameplay of the app with support and troubleshooting as required.

Delivery

The intervention is delivered individually through a combination of 1:1 telephone guidance and app use at the participants' own time. In the first instance, participants will be directed to a dedicated study website to watch a 2-minute video that provides an overview of the app and how to use it. They will then attend a 1:1 brief telephone "on-boarding" session with a counsellor in which the counsellor offers an overview of the intervention and explores the participant's prioritized problems. The counsellor will also provide the participant with a 4-digit app download password to download the app from the study website onto their own/shared family device. The app will be offered to participants for use at their own time over 4 weeks for a suggested minimum duration of 30 minutes per week. The app guides participants through the Adventures and My POD sections, and participants can choose to work on 1 or more self-nominated problems. They are encouraged to work at their own pace through all of the Adventures content, and with respect to at least 1 prioritized problem in My POD, over 4 weeks.

For the duration of the study period, participants will receive a weekly reminder SMS text message containing words of encouragement to use the app. They will also receive a notification to use the app if they do not log in for 5 consecutive days. On-demand telephone support from a counsellor will be available for addressing technical problems and clarifying app content throughout the study. A troubleshooting guide on app installation, resetting passwords, internet problems, and contacting the study team will be available for participants to access on the study website.

Each participant's progress through the app will be visible to their allocated counsellor via a secure web portal. During the fourth week of the intervention or on completing the app contents, whichever is first, a brief "review" call will be arranged between the counsellor and participant via text message or a phone call to discuss the participant's progress, overall learning, and their plan for managing future problems. Participants who require additional help after completing the intervention will be provided with a self-referral sheet containing information about local and national mental health services.

Counsellors

Guidance will be provided by 2 bilingual English- and Konkani-speaking lay counsellors. They have 2 years of experience in delivering a face-to-face (analogue) problem-solving intervention [17] and 1 year of experience in facilitating use of the POD Adventures app in school-based group sessions [18]. Although college graduates, the counsellors do not possess formal training in psychotherapy or experience beyond the scope of low-intensity problem-solving. The counsellors have received initial 4-day office-based training built around a structured intervention manual.

Counsellors will offer individual guidance to each participant and will comprise the scheduled on-boarding and review calls. In addition, counsellors will proactively make telephone calls to participants who do not use the app despite reminders.

Supervision will consist of weekly peer group supervision meetings (lasting approximately 1 hour), moderated by a psychologist. In each meeting, the counsellors will discuss progress of individual participants, review fidelity checklists

of on-boarding and review sessions, and identify areas where troubleshooting or support might be required by any participants.

Control Arm

Through the study website, participants will be sent a digital flyer consisting of information and contact details about local mental health service providers and 2 recently established government provided/affiliated helplines [23,24].

Measures

Participant Characteristics

At baseline, we will collect descriptive sociodemographic data about the selected school populations and adolescents registering for the study. Students will provide their name, phone number, gender (male or female), date of birth, email address (optional), grade, home address, parent/guardian contact information, school name, and how they learned about the study. Enrolled participants will also be asked to respond to 4 questions about their mobile phone and internet use relating to ownership and frequency of use.

Feasibility Outcomes

Feasibility of research procedures will be assessed through routinely logged numbers and proportions of eligible/ineligible self-referrals (with reasons for ineligibility), assenting/consenting participants (with reasons for not assenting/consenting), randomized participants (with reasons for not randomizing), and completed outcome assessments (with reasons for noncompletion).

Feasibility of the intervention delivery will be assessed using data on attendance, intervention completion (ie, attendance at on-boarding and review telephone calls and use of the POD Adventures app) and counsellor-completed fidelity checklists of on-boarding and review discussions.

Intervention processes will be assessed through the number and duration of contacts with counsellors, number of days between on-boarding and review sessions, amount of app content completion, and reasons for non-completion. Data about participants' use of the app will also be captured securely from integrated analytics software. Key indicators will include login and logout timestamps, knowledge of problem-solving assessed through multiple-choice quizzes, and self-reported use of problem solving in real-world situations.

User satisfaction data will be obtained from participants in the intervention arm at 6 weeks using an 8-item service satisfaction questionnaire [25] with 4 appended forced-choice items that ask specifically about the experience of using the POD Adventures app.

After the follow-up assessment, semistructured qualitative interviews will be conducted with approximately 10-15 participants sampled purposively in accordance with sex and age from both study arms; the exact number of interview participants will depend on thematic saturation. Interviews will be carried out over the telephone by a researcher who has not been involved in intervention delivery. Participants will be asked about their experiences of internet-based research procedures such as recruitment, use of the study website, consent, and assessment procedures. Intervention arm participants will be asked additional questions about acceptability of using the intervention on the internet, their experiences of guidance from counsellors, usability and utility of app features, and potential harms. Interviews will be audio-recorded and transcribed by a member of the study team.

Clinical Outcomes

Clinical outcomes will be assessed using 2 validated self-report questionnaires that measure psychosocial problem severity (Youth Top Problems [YTP]) [26] and self-reported depression and anxiety (Revised Child Anxiety and Depression Scale–Short Version [RCADS-25]) [27]. Assessments will be carried out at two timepoints: prerandomization at baseline and postintervention follow up (6 weeks after randomization). Measures will be collected on the internet through the study website.

Sample Size

We used a confidence interval approach for the calculation of sample sizes for external pilot randomized controlled trials [28] which recommend a sample size of at least 70 participants (35 per arm) to estimate the standard deviation for a continuous outcome with good precision for a pilot RCT.

Recruitment and Consent Procedures

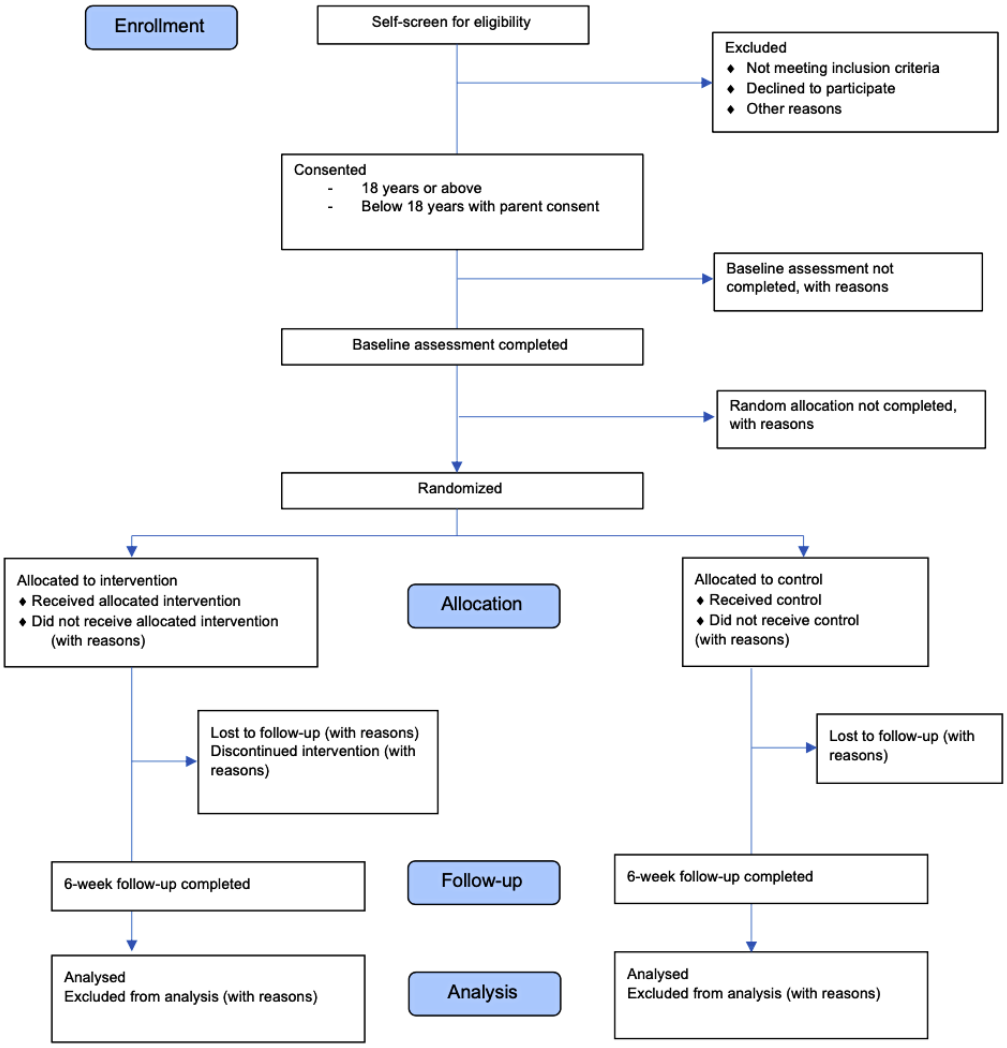
The participant flow diagram is shown in Figure 1. The sampling frame consists of all students from relevant classes in the participating schools. Recruitment will be initiated using (1) a brief 20-30–minute sensitization session delivered to individual classes either on the internet (via virtual classrooms) or, where social distancing policies allow, in school using a slideshow and brief video containing information about the study; and (2) distribution of an electronic or printed information flyer via school-moderated email/WhatsApp groups explaining the study and how to participate.

Interested students will be invited to visit the study website [29] where they will first be required to complete an eligibility assessment in accordance with the study inclusion criteria. If the student is eligible, he/she will be able to watch an animated video about the study and read information about what study participation will entail. Ineligible students will be provided with a digital information flyer that includes details about local and national services and helplines. This will be provided in a language of their choice (English, Hindi, or Konkani).

As part of the study registration process, eligible participants will be asked to provide basic demographic details and create a password for their use of the study website. Following registration, we will obtain digital consent from participants aged >18 years and assent from those aged <18 years. Parent /guardian ("caregiver") consent will also be obtained for participants aged <18 years. Prospective participants and caregivers (if the index adolescent is aged <18 years) will be presented with information in writing, supported by an audio soundtrack in a preferred language, on the study website. The information will be followed by a series of "yes" and "no" questions to establish understanding and willingness to enroll in the study, and verified with a digital signature. For assenting

participants below 18 years of age, digital parental consent will be followed by a confirmatory telephone call to the parent/guardian from the study team within 2 working days. A toll-free helpline will also be made available for prospective participants to ask specific questions and seek technical support for registration.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram that will be used to illustrate participation throughout the phases of the POD Adventures pilot trial.



Allocation and Randomization

Each participant will be allocated a unique, anonymized ID number after registering on the study website. Upon completion of consent, a notification will be sent to the study data manager via a secure web portal designed for the study data collection. Randomization will be performed by the data manager on this platform, and the outcome of allocation will be communicated to the participants through a telephone call from a researcher and through an SMS text message alert, both of which will inform the participant to log in to the study website for information about their allocation. The study website will create a personalized dashboard that directs the participant to their next step.

The randomization algorithm will be computer-generated and stratified by school grade using randomly sized blocks of 4, 6, and 8. Participants and counsellors will not be blinded to the allocation assignment. However, other members of the research team (the principal investigator, trial statistician, and researchers) will remain blind to participation allocation status.

Data Collection

Screening and Initial Assessments

The schedule for enrollment, interventions, and assessments is summarized in Table 2. Participants will complete a self-screen for eligibility and then register on the study website. They will receive an automated SMS text message alert to complete the baseline assessment once assent/consent is received. A researcher will make contact via telephone to remind the participant if the baseline assessment has not been completed 2 days thereafter. The measures take approximately 15-20 minutes to complete on the internet. Researchers will make up to 4 telephone attempts over the subsequent 2 weeks.

Table 2. Schedule for enrollment, interventions, and assessments.

Timepoint	Enrollment (7 working days)	Allocation (0 weeks)	Follow-up at 6 weeks post randomization
Enrollment			
Self-screener for eligibility	✓		
Informed assent (participant) and consent (parent/guardian)	✓		
Allocation			
Interventions			
POD Adventures		✓	
Usual care information		✓	
Assessments			
Demographic information	✓		
Outcome assessments (self-reported)	✓		✓
Youth Top Problems (YTP)			
RCADS-25			
Process evaluation			
Service satisfaction questionnaire			✓
App process data (intervention arm)			
Qualitative interviews	✓	✓	✓
Research and intervention process data			

Follow-up Assessment

Participants will receive an SMS text message reminder 42 days (ie, 6 weeks) post randomization to complete the follow-up assessment on the study website. This will be accompanied by a telephone call from the researcher using a standardized script that asks participants to complete the assessment. Automated SMS text message reminders will be sent to the participants every 3 days over the next 2 weeks or until the follow-up assessment is completed on the study website. Researchers will make up to 4 telephone attempts following this due date, with a maximum allowance of 2 weeks.

Qualitative Interviews

Within 2 weeks of completing the follow-up assessment, a subsample of participants, purposively selected from both trial arms, will be invited via telephone to take part in an interview.

Strategies for Promoting Participant Compliance, Retention, and Completing Follow-up

Intervention participants' attendance at scheduled telephone sessions will be logged by counsellors. We will also undertake the following activities to support adherence to study procedures in both trial arms:

1. All participants will receive an SMS text message instruction to complete their baseline and follow-up assessments, along with SMS text message notification once this is completed.
2. All participants will receive a telephone call from a researcher 2 days after the first SMS text message alert with an invitation to complete the baseline assessment and as soon as their follow-up assessment is due.
3. If a participant cannot be reached by telephone after 4 consecutive attempts, they will be sent an SMS text message and asked to opt in for any further contact.
4. Participants in the intervention arm will receive an SMS text message reminder 1 day prior to on-boarding and review telephone sessions.
5. All telephone calls and SMS text messages, successful and unsuccessful, will be documented.

Data Security and Management

The study will be hosted on the servers of Sangath, the implementing organization based in Goa, India. These servers will be encrypted, with data backups occurring daily. The study web portal and its associated data will be accessible only to authorized and approved personnel. When registering, participants will create password-protected accounts and the platform allocates a unique trial IDs to participants. For analyses, data will be deidentified by removing names, contact information, and any other personal identifiers. Students who withdraw from the study will have their data deleted and a withdrawal confirmation notification will be sent from the research team by telephone or email. All data will be stored securely for 10 years.

Monitoring and Safety

Data Monitoring

Monitoring and governance for the pilot trial will be provided by a Trial Steering Committee (TSC; comprising senior investigators and independent subject experts) and Data and

Safety Monitoring Committee (DSMC; a fully independent group with relevant clinical and trials expertise). Any study protocol amendments will be agreed and formulated in conjunction with the TSC and DSMC and submitted to relevant institutional review boards for approval.

Harms

The study team will continuously monitor for any participant safeguarding concerns. At baseline, all participants will be screened for risk of self-harm or suicide. Risk will be identified using a brief screening questionnaire followed by a telephone-based structured assessment where indicated. If a participant reports the presence of any thoughts of self-harm or suicide during the baseline assessment or during on-boarding or review phone calls (intervention arm participants), a risk management session will be provided to the participant within 24 hours along with information about support services will be immediately provided by the counsellor. If deemed appropriate by the clinical supervisor, the participant will also be referred to an independent mental health specialist for further assessment/treatment. At the 6-week follow-up assessment, all participants will be asked about any negative effects of using the intervention or participation in the study more generally.

COVID-19 Precautions

The research team will implement the pilot trial in line with local and national public health guidance and make every effort to minimize in-person visits to schools unless specifically requested by schools. Health and safety measures outlined in local government guidelines for school reopening will be strictly followed by research staff who may visit schools as part of any recruitment activities. In addition, fieldwork safety training will be provided to all study team members. Study team members will employ measures to maintain physical distancing and use of personal protective equipment such as masks in line with local health and safety protocols.

Analyses

Statistical Analysis

The statistical analysis for this pilot trial will be mainly descriptive in nature, aiming to provide estimates of key trial parameters and to inform power calculations for a future trial. The outcome measures will be summarized at baseline and at 6-week follow up by trial arm. These will be summarized by mean (SD), median (IQR), or n (%) values as appropriate to relevant subgroups (defined by age, gender, and baseline outcome score). For continuous outcomes, histograms will also be plotted within each arm to assess normality and whether any transformation is required.

Analyses will be conducted to examine the effect of the intervention in normal and clinical subgroups (as measured by the RCADS-25).

Qualitative Analysis

Qualitative interviews will be transcribed verbatim and downloaded to NVivo (version 12, QSR International). Thematic coding frameworks will be constructed to allocate codes to emergent themes within the data, facilitating their identification and organization. Transcripts will be independently coded to enable discrepancies to be identified and consensus reached about the interpretation and application of the coding framework. Data that do not fit the initial coding framework will lead to the generation of new themes and framework revision. Data will then be consistently classified, indexed, and subject to thematic analysis using the refined coding framework.

Ethics and Safety

Institutional review board approvals have been obtained from the Indian Council of Medical Research (ICMR); Sangath (the implementing organization in India); Harvard Medical School, Boston (Massachusetts, United States; the sponsor), London School of Hygiene and Tropical Medicine, United Kingdom (collaborator); and the University of Sussex, United Kingdom (collaborator). Permissions from individual institutions have also been obtained for all participating schools.

The principal investigator will act as the custodian of the data in accordance with the legislation of the research sponsor (Harvard Medical School) and funder (Wellcome Trust, United Kingdom).

Dissemination Plan

School reports, consisting of the mean aggregate scores for the measures, will be prepared and shared with the school at completion of the data collection period. The study results will be prepared for academic publication in open-access mode.

Results

Student sensitization sessions began on the internet and in person on January 11, 2021. The first participant was enrolled on January 28, 2021, and his/her 6-week assessment was completed on April 4, 2021. Owing to a second wave of the COVID-19 pandemic in India, schools in Goa were closed on April 22, 2021. At the time of manuscript submission, trial participants are receiving the intervention or completing follow-up assessments, with all activities carried out remotely.

Discussion

This paper describes the POD Adventures pilot trial, which aims to assess the feasibility of conducting a future large-scale trial of a gamified mental health intervention for secondary school students in India. Designed as an early intervention for common youth mental health problems, POD Adventures is intended to meet the growing need for mental health support among secondary school students in India [30]. All intervention and research activities have transitioned to the internet in the context of COVID-19 restrictions. The results will therefore offer specific insights into the viability of delivering and evaluating psychosocial interventions under conditions of social distancing and school closures.

An individually randomized design was chosen for this study owing to the relatively small number of available schools, which ruled out an alternative cluster-randomized design. Risks of contamination are minimized through remote internet-based delivery, which limits potential for communication between participants that might ordinarily occur in school settings. Additionally, the choice of a usual care control, consisting of

information about other services and helplines, rules out the possibility of contamination due to the same counsellors interacting with both trial arms [31].

Key challenges of this study may be uptake and adherence. Despite the compulsory transition to internet-based education for students across India, there are still variations in smartphone ownership and access to internet connectivity [32]. Young people from high-income settings have reported many challenges impacting on their engagement with internet-based interventions, such as limited access and technical issues, lack of time, doubts regarding the perceived helpfulness of the program, and preferences for face-to-face help [12]. Further, delivery of self-directed digital programs for youth at home and in other relatively unmonitored settings has been associated with relatively poor adherence [33]. A recent review of studies from Latin America showed similar challenges [34]. Low mental health literacy in our demographic may be another factor that may negatively impact uptake [35]. In anticipation of these challenges, the study uses a broad range of recruitment strategies aligned with existing best practices [15], such as in-person classroom sensitization (where possible), use of explanatory videos and flyers, and use of a toll-free telephone number for queries.

Competing demands for time may be another engagement barrier and has been previously observed in PRIDE studies conducted in Indian schools [16,18]. Counsellor guidance and reminders via SMS text messaging or app notifications offered to participants in the intervention arm may positively impact retention [36]. Looking beyond the immediate context of this study, potential implementation barriers include a shortage of suitably trained, supervised, and motivated school counsellors. To address this concern, a separate component of the wider PRIDE research program will examine the effects of a digital training curriculum on competences of prospective school counsellors to deliver an evidence-based problem-solving intervention.

The strengths of this pragmatic pilot trial include the novelty of the intervention and its pivot from in-person to internet-based delivery in a low-resource setting. Outcomes will be assessed via self-report, thereby lowering the risk of bias due to unblinded outcome assessments. The study should offer useful insights about the feasibility of remotely delivered mental health interventions for adolescents in similar contexts.

Acknowledgments

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Authors' Contributions

PPG, DM, and VP conceptualized the study. PPG led on drafting the protocol, with critical inputs from DM and VP. HAW contributed to the statistical analysis plan. PPG, BB, RS, and AJ contributed to the coordination of the trial. EH, CF, PC, and KC contributed to the refinement of the protocol. All authors read and approved the final manuscript. DM and VP contributed equally as senior authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention modifications for remote online delivery.
[DOCX File , 17 KB - resprot_v10i10e30339_app1.docx]

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Abbreviations

DSMC: Data and Safety Monitoring Committee
ICMR: Indian Council of Medical Research
RCADS-25: Revised Child Anxiety and Depression Scale–Short Version
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TSC: Trial Steering Committee
YTP: Youth Top Problems

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Protocol

Assessing the Feasibility of a Multicenter Transition Intervention Model Across Adolescent Secure Services in England (MOVING FORWARD): Protocol for a Feasibility Cluster Randomized Controlled Trial

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Abstract

Background: Young people moving from adolescent secure inpatient units to adult care in the United Kingdom have multiple and complex needs and are more likely to experience poor transition outcomes. Poorly managed transitions can lead to enduring use and dependency on mental health services. However, there is a lack of knowledge about the feasibility of transitional care models.

Objective: This paper presents the protocol for a study that aims to test a feasibility cluster randomized controlled trial for young people transitioning from adolescent secure services to adult-oriented settings. The overarching aim of the MOVING FORWARD study is to provide a preliminary estimate of the effectiveness and cost-effectiveness of a new transition intervention model and to inform a future full-scale cluster randomized controlled trial.

Methods: The design of the study is a 3-arm feasibility cluster randomized controlled trial comparing the MOVING FORWARD intervention against standard transition preparation conducted at 6 adolescent secure services, of which 4 units will receive the intervention and 2 will serve as controls. Eligible young people between 17-19 years, their parents/carers, and key workers will be invited to participate. Young people and parents/carers will be allocated to two conditions (young people alone and young people with a parent/carer) and will receive 4 transition preparation workshops across 6 months. Six adolescent secure hospitals will be randomly allocated, stratified by area and service type. Data will be collected at 3 time points: baseline (T0), 6-12 months postintervention (T1), and 18-24 months postbaseline (T2). Primary and secondary outcomes will be based on assessment measures and interviews conducted at T1 and T2.

Results: A total of 13 young people and 17 staff members have contributed to the intervention design through online advisory groups on the design of the study and important themes for transition. We have also consulted members of the public (a steering group) including 2 young people who have transitioned to the community and 2 parents/carers. Common identified themes included appropriateness of module content and support during delayed transitions. The content of the intervention will be finalized during the first 6 months of the study. Participants will be recruited over the course of 6 months. An intraclass correlation coefficient will be calculated to inform the power of the sample size for a further large-scale trial. With a sample size of 50, we will be able to estimate a dropout rate of 80% (95% CI –11% to 11%).

Conclusions: This research will provide practitioners and policy makers with an evidence-based framework of how training and familiarization with the prospective transitions can yield positive outcomes. This study will test whether a psychosocial intervention can be implemented in adolescent secure hospitals. The results will identify barriers and facilitators to the proposed intervention and will enable services to reflect on the quality of transitional care delivery.

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KEYWORDS

transition; intervention; young people; feasibility cluster randomized trial; cluster randomized controlled trial; secure hospitals; outcomes; adolescents; patients

Introduction

Background

Previous research has classified transitions as a global priority for chronic conditions [1]. There is substantial evidence that transitions from pediatric services to adult care in the United Kingdom are linked to the exacerbation of medical and mental health symptoms and poor life opportunities [2]. Young people moving from inpatient (tier 4) child and adolescent mental health services to adult-centered settings are more likely to experience poorly planned transitions due to inconsistent care and low transition readiness [3]. Fundamental differences in treatment approaches and care priorities have created a substantial gap between child and adult services and, coupled with low transitional readiness, have been found to be major barriers to positive transition outcomes [4]. Transitional care is particularly poor for young people in adolescent secure services, most of whom are detained under the jurisdiction of the Mental Health Act due to offending, and present with multiple comorbidities (including emerging personality disorders, neurodevelopmental and learning disabilities, and psychosis), for which many already experience prolonged stays in hospital [5]. As of 2016, there were 1283 young people in secure hospitals across England; approximately 43% of this cohort did not have a placement address when transitioning to the community [5]. Adolescents in these services, including medium and low secure units and psychiatric intensive care units (PICUs), constitute a neglected research and clinical group despite their multitude of needs and disadvantage (social adversity, trauma, high risk, and vulnerability).

Young people in contact with the youth justice system are more likely to experience multiple transitions across a range of services, including secure establishments to secure inpatient hospitals [6]. Six percent of young people in secure care have been in 10 or more placements before moving to inpatient secure hospitals [5]. Each setting follows different principles in their care approach and delivers different treatment models to the young people they accommodate. These constant changes in principles and care are particularly harmful and challenging for young people with learning disabilities, autism [6], and other neurodevelopmental disorders.

The Need for a New Transition Model

There remains a dearth of research aiming to develop, implement, and evaluate transitional care models [6]. Effective and supportive transitions foster independence in young people and facilitate confidence in their treatment. The National Institute for Health and Care Excellence (NICE) 2016 guidelines explicitly state that self-efficacy (managing one's own health) is a key priority for service commissioners and policy makers, and recommend evidence-based research in the form of cluster randomized controlled trials (cRCTs) in self-management training to improve transition preparation for special groups [7]. This study aims to address this gap and improve current processes for young people transitioning from adolescent secure services to adult-oriented care by (1) developing a psychosocial transition intervention with a developmental focus and (2) assessing the feasibility of undertaking a future trial of its clinical and cost-effectiveness.

Fragmented support during transitions can lead to enduring use and dependency on mental health services pertinent to long-term financial burden, limited employment opportunities and social functioning [8], as well as high reoffending rates and reinstitutionalization [5]. As such, transitional care has become a national priority in the United Kingdom to minimize the risk of poor transition preparation and increase positive outcomes. Recently developed practice guidelines on care transitions from adolescent secure services to adult services stress the importance of graded and flexible transitions aiming for a needs-based care model, contrasting to the age-based approach currently in use [9]. However, most available interventions are in line with adult models of care and may fail to include developmental perspectives [5], and there are no interventions or guidance targeting transitional care in secure settings. In addition, there remains a lack of well-defined planning and knowledge about the feasibility of specific models of transitional care that can reduce the public health burden of emerging adults at risk. The implementation of systematic interventions during institutional and health care transitions is highly likely to be cost-effective considering the costs associated to enduring mental health issues and secure hospital admission. This research is timely and falls within the scope of the National Health Service (NHS) Five Year Forward View in implementing new models of care for young people within the capacity of "personalized care" and borne from coproduction, whereby individuals are empowered using a strength-based approach. The research also aligns with the NICE 2016 guidelines, the Care Act 2014, the National Institute for Health Research (NIHR) infrastructure, and the NIHR Applied Research Collaboration South London, aiming to improve health care services for young people.

Evidence for the Proposed Intervention

The proposed developing intervention is based on previous effectively established and implemented intervention models, including cognitive behavior therapy (CBT), parent-child interaction therapy, attachment-based therapy, social skills training (SST), and psychoeducational elements, which target self-efficacy and management of mental health and conduct problems tailored around goal-oriented approaches. SST and CBT group-based interventions are particularly effective in young people with autism [10]. Elements from these

well-established approaches will contribute to behavior change in young people in secure care via upskilling them and building a goal-oriented approach toward their discharge. For example, elements from attachment-based and trauma-informed models will be used to increase confidence among young people and facilitate the "letting go" process. There is compelling evidence that these therapeutic models are effective for young people with challenging behaviors and complex trauma histories like those in secure care [11-14]. The current intervention will contribute to self-efficacy upon discharge. Key transition workers will be trained to deliver this intervention considering they are key attachment figures for young people. The intervention will start 6 months before they turn 18 years of age to allow time to prepare and avoid abrupt transitions. These interventions are more likely to be brief and successfully delivered in clinical settings, as in the proposed feasibility trial [13]. Group-based interventions delivered to young people with neurodevelopmental needs and mental health problems have shown increased self-determination and social functioning [15-18].

Aims and Objectives

The MOVING FORWARD study aims to implement a new transition intervention model for young people transitioning from adolescent secure services to adult-oriented settings and test the feasibility of a future cluster trial measuring its effectiveness. The primary objectives are (1) to finalize the development of the intervention; (2) to determine the feasibility of conducting a full cRCT in adolescent secure inpatient units; (3) to test the feasibility and acceptability of trial procedures and materials, including recruitment, randomization, allocation, assessment tools, response rates, adherence and follow-up across 6 sites; (4) to determine the appropriateness of the proposed outcome measures; (5) to describe treatment as usual (controlled condition) across all sites; and (6) to qualitatively explore the views and experiences of health care staff delivering the intervention.

Methods

Intervention Development

Figure 1 illustrates the coproduction plan and refinement process of the MOVING FORWARD intervention [19]. The intervention is in the process of development and will be finalized in the first 6 months of the study with the help of the steering and stakeholder groups, which were set up in the first and second stages of the coproduction phases. As of July 2021, the advisory groups have agreed on the overarching themes leading the 4 workshops: transition literacy; future plans; goal management; and expectations, attachment, and self-efficacy (Table 1). This research builds on an early career researcher grant awarded by Kingston University, which established advisory groups to coproduce a transition intervention for young people transitioning from adolescent secure services to adult services and their families. Advisory groups were set up with 13 young people with a previous, current, or upcoming transition experience from adolescent secure services to adult services, 2 parents of young people who had experienced this transition, and 17 staff from adolescent secure services. This study aims to implement this modular intervention and test the feasibility of a full clinical trial.

Figure 1. Development and refinement of the MOVING FORWARD intervention.

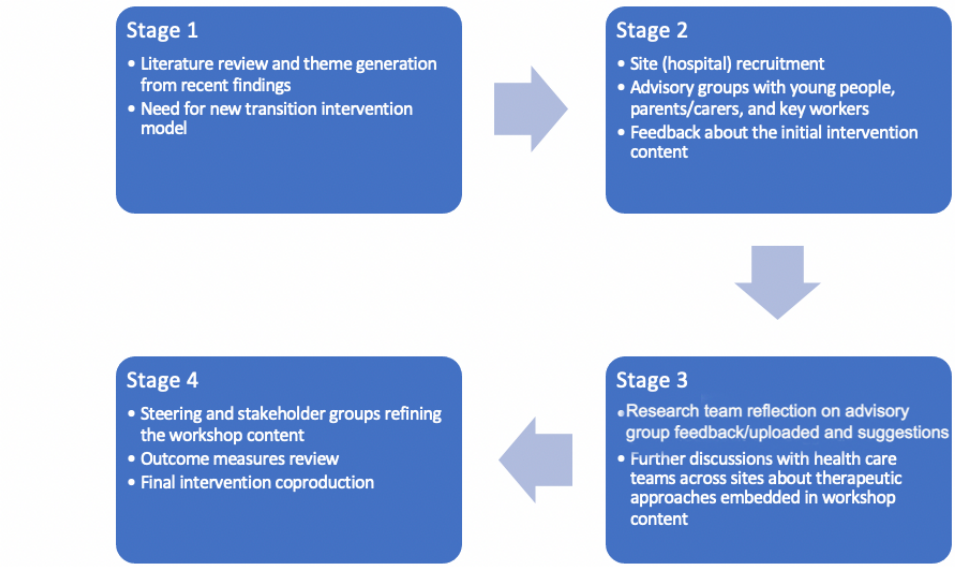


Table 1. Intervention themes and workshop content.

Intervention	Theme	Aims	Module tasks
Workshop 1	Transition literacy	Participants will be asked whether they understand the purpose of moving to adult services or an adult-oriented community and how they envision a positive transition. The elicited themes will inform the subsequent stages of the intervention	Role playing, vignettes/scenarios, videos, reflective discussion and writing, skills management
Workshop 2	Future plans	Participants will focus on education, employment, overall well-being, housing, and community living	Role playing, vignettes/scenarios, videos, reflective discussion and writing, skills management
Workshop 3	Goal management	Participants will be introduced to mental health symptom and risk management when in crisis, relapse and reintegration, support services, peer support, and role models and mentors	Role playing, vignettes/scenarios, videos, reflective discussion and writing, skills management
Workshop 4	Expectations, attachment, and self-efficacy	Participants will focus on what to expect in adult services, what difficulties they might encounter, what being an adult encompasses, what new responsibilities they will face depending on the type of placement they are admitted to, how the therapeutic style and alliance might change, parental involvement, hospital/community routine and structure, and older peers	Role playing, vignettes/scenarios, videos, reflective discussion and writing, skills management

Feasibility Trial Design

This study is a mixed methods, multicenter, 3-arm, feasibility cRCT with a parallel design comparing the MOVING FORWARD intervention against standard transition preparation (usual care: Care Programme Approach [CPA] discharge and individual meetings with the responsible clinician) conducted at 6 adolescent secure sites, of which 4 units will receive the intervention and 2 will serve as controls. Young people across these adolescent secure services present with similar mental health and neurodevelopmental needs and complex trauma history. In this specific study, we will focus on those with emerging borderline personality disorder, psychosis, autism, learning disabilities, and conduct disorder. Data will be collected at 3 time points: baseline (time 0; T0), 6-12 months postintervention (time 1; T1), and 18-24 months postbaseline (time 2; T2). A cRCT will minimize the risk of contamination, which is high in the proposed study as elements from the intervention could be used for standard transition preparation.

A feasibility study will measure the acceptability of conducting a future, fully powered trial across different pools of young people in secure care and different settings across adolescent secure hospitals. This study will test how the future trial will look like, as well as the main research question and primary outcomes. Outcome measures and one-to-one semistructured interviews with young people, parents/carers, and health care staff will be conducted to explore the experiences of young people receiving the intervention and those who received treatment as usual (TAU). The practicality and integration of the intervention within the current system of care and use of resources will be explored with the participants. A total of 30 interviews will be sought to understand the mechanisms of impact.

Training of Health Care Staff

A transition workshop will be delivered to a group of health care staff about preparing young people moving to adult services based on predetermined themes during the staff advisory group meetings (transition management, plans in action, coordination with receiving services, joint working, continuity of care, structural problems, infrastructural weaknesses, a structured health transition plan based on individualized needs, education in line with CPA reviews). This workshop will train health care staff to deliver the developing intervention to the young people who have agreed to participate in the study. Those delivering care as usual will not receive training. Health care staff will receive training 3 months pretransition in the form of two 45-minute workshops. The training will be standardized to increase intervention fidelity.

Trial Conditions

Condition 1: T0 Baseline Pretransition (6-12 Months Before 18th Birthday)

As discussed with the advisory groups in the first stage of the coproduction/development phase, this intervention will include 4 modules delivered over 8 series of 2-day workshops. When the intervention is finalized, a manual will be developed including the goals and objectives of each workshop, skills developed, behavior expectations and management, themes that need to be covered, required materials for the sessions, and strategies for young people with neurodevelopmental needs. The content of the sessions will be the same across different groups of patients although adjustments will be applied to the intervention models based on each group's mental health and developmental needs identified during the piloting phase with the lead sites (Ardenleigh and St Andrews). These adjustments will be discussed with the steering group to ensure that the intervention fidelity is not threatened. Additionally, monitoring procedures with the help of the research team across the study will enhance intervention fidelity. For example, young people with neurodevelopmental needs may need additional help in terms of mental health literacy and understanding the purpose of their prospective transition. The workshops will be delivered across 4 days, and there will be 4 sessions targeting different domains of transition. Staff members who attended the transition training will deliver these workshops as they are key attachment figures to the young people. Each workshop will take between 30-40 minutes. Key workers from the advisory groups suggested that the intervention should be informed by attachment-based

therapy, CBT, SST, and psychoeducational elements, which target self-efficacy and management of mental health problems.

Condition 2: T0 Baseline Pretransition (Young People and Parents/Carers)

The same series of workshops will be delivered with involved parents/carers to examine whether parental involvement in the process yields different outcomes.

Condition 3: T0 Baseline Pretransition (TAU)

This group of young people will receive TAU (standard transition care through the CPA) depending on the service, which may or may not involve transition preparation.

Conditions 1-3: T1 (6-12 Months Posttransition)

Young people and parents/carers (condition 2) who received an intervention and those who received care as usual (condition 3) will be visited and interviewed at the receiving placement 6-12 months postdischarge. Outcome measures will be completed.

Conditions 1-3: T2 (18-24 Months: Endpoint)

Young people and parents/carers (condition 2) who received the interventions and those who received care (condition 3) as usual will be followed up depending on an old or new placement and will be interviewed about continuity of care, mental health, overall well-being, education, employment, and relapse. Outcome measures will be completed.

Allocation Strategy

The adolescent secure service is the unit of randomization and will be randomly selected until 6 sites are recruited. Sites were eligible if they provided low or medium secure care, or they were classified as PICUs. Six adolescent secure hospitals will be randomly allocated into 1 of 3 arms in a 1:1:1 ratio, stratified by area (south versus north) and type (medium versus low versus PICUs) first. Then participants at each site will be allocated to the same treatment. A total of 4 secure units will be allocated to the intervention arms and 2 units allocated to the control arm. Allocation will be performed (computer-generated allocation) by an independent member of the team who will be blind to the identity of the unit. Considering the nature of the intervention, young people and health care staff will not be blinded. The statistician and all team members collecting follow-up data, apart from the principal researcher and fieldworkers, will remain blind to the allocation of the units to trial arms.

Participants

Young People

A total of 50 participants will be recruited on a rolling basis over 6 months from the commencement of the study. Any young person meeting the inclusion criteria listed below irrespective of their gender, ethnicity, religion, education, and disability status will be eligible for inclusion:

- If aged ≥17 years and eligible for transition from an adolescent secure hospital, including those experiencing delayed transitions;
- If formally diagnosed with a mental disorder, and/or learning disability, and/or neurodevelopmental problem.

Any young person meeting the following criteria will be not eligible for inclusion:

- If presenting with moderate intellectual impairment with an IQ<65;
- If in an acute phase of severe mental illness;
- Cannot provide consent due to physical disabilities and/or language problems or any other neurodevelopmental deficits.

Parents/Carers

A total of 20 parents/carers will be recruited pre-, during, and posttransition. Family therapists, responsible clinicians, and social workers from participating adolescent secure services will facilitate this process. A random sample of parents/carers will be interviewed at T1 and T2.

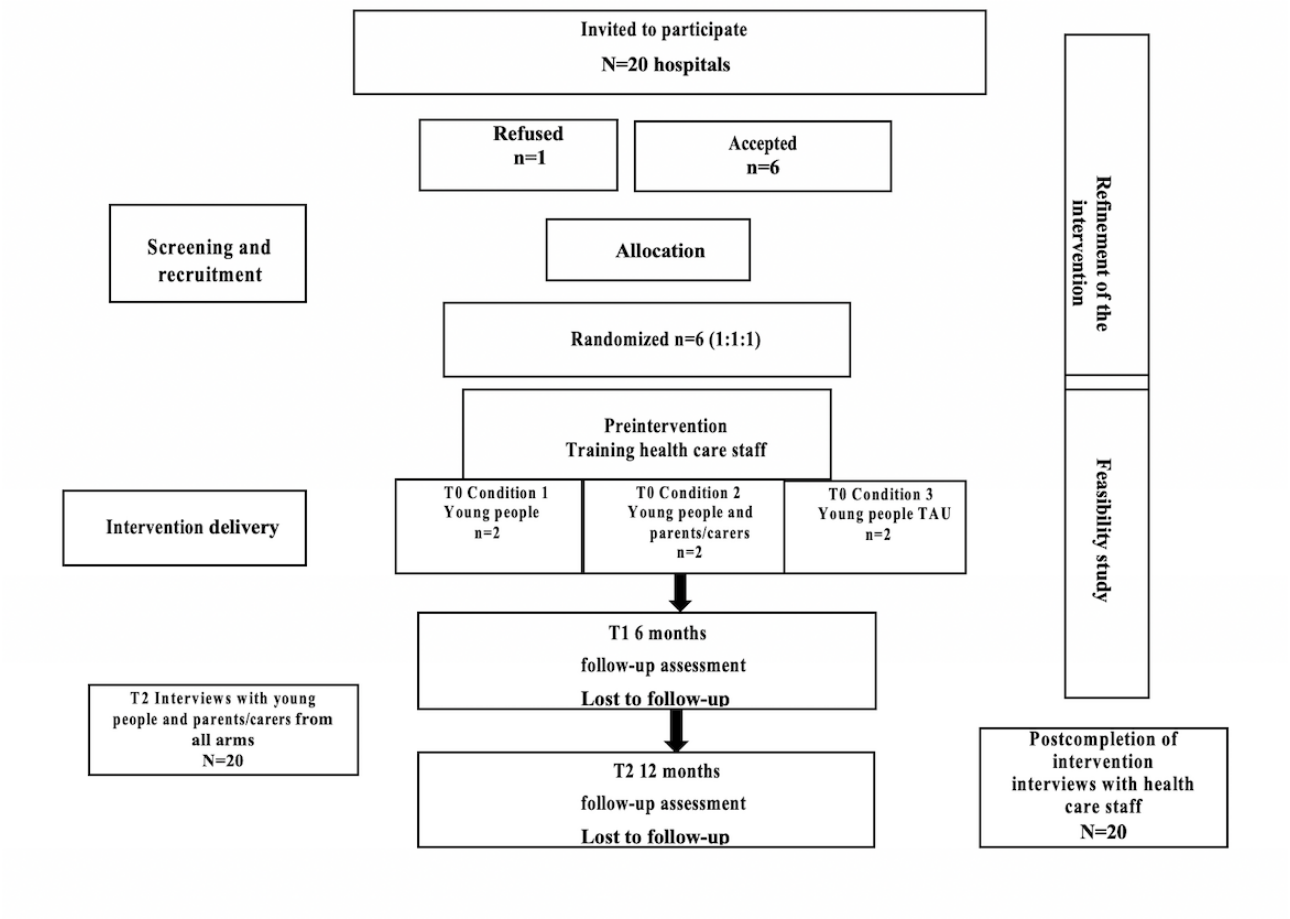
Health Care Staff

A total of 30 multidisciplinary team members will be sought for recruitment during the different phases of the study. Key workers involved in the transition planning, such as responsible clinicians, psychologists, family therapists, occupational therapists, social workers, nurses, and health care support workers, will be recruited. A random sample of health care staff will be interviewed postintervention delivery at T1.

Recruitment and Support

The research team will be informed by health care staff at each site about the young people's eligibility and capacity to provide written informed consent. The local collaborator will introduce the study to all eligible young people with the help of a study leaflet, a visit or virtual meeting by the research team (to account for COVID-19), and posters advertised at each site. The information leaflets will consider young people's developmental, language, and learning impairments. The "Bonding Plan," which was adopted by the MILESTONE study (the largest European transition trial) will be used as a retention strategy with some minor adjustments depending on the setting. For young people in the community, gift vouchers will be provided. For those in secure hospitals, a voucher will be transferred to their account so that they can use it once they are released. Figure 2 presents more details.

Figure 2. Diagram of the feasibility cluster randomized controlled trial. TAU: treatment as usual.



Sample Size

An intraclass correlation (ICC) coefficient will be calculated to inform the power of the sample size for a further large-scale trial. A statistician based at the joint Faculty of Health, Social Care and Education at Kingston University and St George's University of London will be involved in the design of the feasibility cRCT. This feasibility study aims to estimate the required sample size for a definitive cRCT evaluation of the intervention. We will estimate the variability in the likely definitive trial outcome (improved mental health and adjustment to adult settings upon follow-up) using an ICC. The sample size of young people may vary between 40 to 60 (8 to 10 young people at each site) and parents/carers 20 to 30 (4 to 5 parents/carers at each site) as recommended [20]. With a sample size of 50, we will be able to estimate a dropout rate of 80% (95% CI –11% to 11%).

Primary Outcome Measures for a Future Trial to Measure Improved Mental Health, Social Functioning, Adjustment, and Quality of Life

The suitability and acceptability of assessment tools will be based on feedback from the steering and stakeholder groups and key workers in secure hospitals a priori and ad hoc and response rates. Additional feedback will be sought from the participants after completion of the following questionnaires:

1. Transition Readiness Assessment Questionnaire (TRAQ) [21] (T0, T1, T2): to measure whether the transition intervention outcomes are linked to transition readiness predischarge;
2. Transition Related Outcome Measure (TROM) [22] questionnaire (T1, T2): to measure whether transition outcomes have improved as a result of the intervention;
3. Adult functioning assessed by the Specific Levels of Functioning Scale (SLOF) [23] (T0, T2): to measure social functioning and evaluate how the intervention has facilitated self-management and efficacy in young people;
4. Subjective well-being assessed by the Personal Adjustment and Role Skills Scale (PARS-III) [24] (T1, T2): to measure psychosocial adjustment–peer relations, hostility, risk in postdischarge, and if the intervention has facilitated the process of psychosocial reintegration;
5. Quality of life assessed by the World Health Organization Quality of Life Assessment (WHOQOL-BREF) [25] (T0, T1, T2): to determine if the intervention has improved quality of life—physical, psychological, and independence level—postdischarge;
6. EuroQol Five-Dimensional Questionnaire, Youth Version (EQ-5D-Y) [26] (T0, T1, T2): to determine if this cost-effectiveness tool is appropriate for a fully powered trial along with the intervention fidelity;
7. Data on preliminary resource use will be collected via semistructured interviews with health care staff, young

people, and parents/carers. Service use schedules may be developed to assess cost-effectiveness.

Analysis Plan

Health Economic Data and Analysis

All resources required to measure the intervention implementation including the time spent by staff in training and on delivering the intervention will be monitored with site visits and allocated local collaborators at each site. The EQ-5D-Y will be used to measure health-related quality of life and its sensitivity will be explored. Considering this is a feasibility study, collected data such as intervention and resource-associated costs will be collected with relevant questions via qualitative interviews (eg, clinical opinion) to inform the economic evaluation for the future full-scale trial.

Quantitative Analysis

Demographic characteristics will be summarized using descriptive statistics. The between-cluster and within-cluster variance will be determined. Sample sizes for a future definitive trial will be based on detecting a difference in outcomes (mental health and risk presentation) between trial arms, estimated using the TROM and based on combinations of different alpha (ie, significance level) and beta (ie, power) rates. The ICC will be calculated using the linear mixed model and will explore correlations between participants within the same cluster, as well as to inform sample size calculation for the definitive trial.

Qualitative Analysis

Recordings of interviews will be transcribed verbatim. Thematic analysis will be performed to identify key themes around transitions. The 6-step approach as suggested by Braun and Clarke [27] will be followed. Predetermined (derived from the literature) and data-driven codes will be used for transcription purposes. These codes will be refined to produce emergent themes. A constructionist approach will be followed to account for the impact of context and personal experiences. The transcripts will be examined for similarities, differences, and patterns. The experiences of young people will be explored to understand the intervention acceptability, implementation, and mechanisms of impact.

Ethics

Approval by the Health Research Authority will be sought for the purposes of this research. The research team has extensive experience with submitting previous applications using the Integrated Research Application System to obtain ethical approval, including for vulnerable groups such as young offenders. Then, each site should provide an honorary contract or letter of access to the research team, facilitated by the Research and Development office at that site.

This protocol was submitted in January 2021 to the NIHR Advanced Fellowship Programme and has been internally and externally peer-reviewed by academic colleagues based at King's College London and Kingston University.

Results

Important Themes Based on Advisory Group Feedback

The advisory groups highlighted themes of particular importance and relevance to the intervention, including communication and parallel care, transition delays, traumatic assessments, familiarity with adult services and key workers, and family engagement, and provided advice about the outcome measures. Young people described transition to adult services as scary, and they were keen to participate in the prospective feasibility study. A young person's recommendation on providing peer support to improve self-management in the community was incorporated in the intervention. These areas have informed key aspects of the intervention, such as the inclusion of parents/carers, and its core modules, which improve the understanding and expectations of transitions and working with goals (described in more detail below and in Table 1).

Timeline and Deliverables

The first year will be used for recruitment, finalizing the intervention, developing the protocol of the feasibility study, and training health care staff. During the second year, we will conduct follow-up assessments and data analysis. The final year will be used for report writing and dissemination of findings through patient and public involvement (PPI) and clinical collaborations to increase impact on policy transition guidelines and standard clinical practice. The deadlines outlined below will be followed strictly to manage the delivery of reports within the designated time frame. Study leaflets have been administered to potential participants already, and local collaborators have informed staff and young people about the feasibility study at all participating sites. Potential risks have been discussed with the advisory groups.

Dissemination and Impact

Advisory group members, all of whom have direct or indirect experience of the transition from adolescent secure services to adult services, have expressed interest in providing PPI throughout the study to improve outcomes in design, data collection, analysis, and dissemination. One young person has been recruited as a member of the research team, and 2 parents and 2 young people have agreed to join the steering group, which will meet twice annually for 3 years. Additional PPI recruitment efforts are ongoing, aiming to recruit an additional young person and parent/carer to the steering group. A stakeholder group will be built including 1 NHS commissioner and 2 health care providers who have agreed to participate. The intervention will be finalized with the help of the steering and stakeholder groups, who will additionally review information sheets, consent forms, and outcome measures to check their appropriateness.

The findings are expected to be presented at national and international conferences, published in peer-reviewed journals, and communicated in regular study newsletters, meetings, and internal conferences at the participating sites. An internal networking event including adolescent and adult secure and community services will be organized to share the findings and receive input about the sustainability and inclusion of the

proposed intervention in standard care. Kingston University in collaboration with the University of Warwick will hold a public dissemination event in which young people will reflect on their transition experiences. The findings will be also shared with NHS England and the Department of Health.

We will additionally work with young people who have returned to their communities, who will be supported to run local events in their catchment area to inform the public in accessible ways (using social media and YouTube) about transitioning to the community from secure care. Young people who have moved to adult secure hospitals will have an equal opportunity of being involved in the dissemination of the findings to their peers and their parents/carers by arranging internal community dissemination events in hospitals. A video will be created by young people who have moved to adult services to showcase to future cohorts.

Progression Criteria and Feasibility Outcomes

A traffic light approach (stop-amend-go/red-amber-green) will be used and discussed a priori with PPI, advisory and local collaborators/key contacts, and research mentors about the following criteria:

- Recruitment: at least 80% of target
- Intervention fidelity: at least 80% of intervention workshops meet the fidelity criteria
- Intervention acceptability: at least 80% of staff can be trained and deliver the intervention (barriers and facilitators to intervention design)
- Follow-up numbers: at least 70% at T1 and 60% at T2
- Acceptability of assessment tools: at least 70% at T1 and 60% at T2

The outputs are as follows:

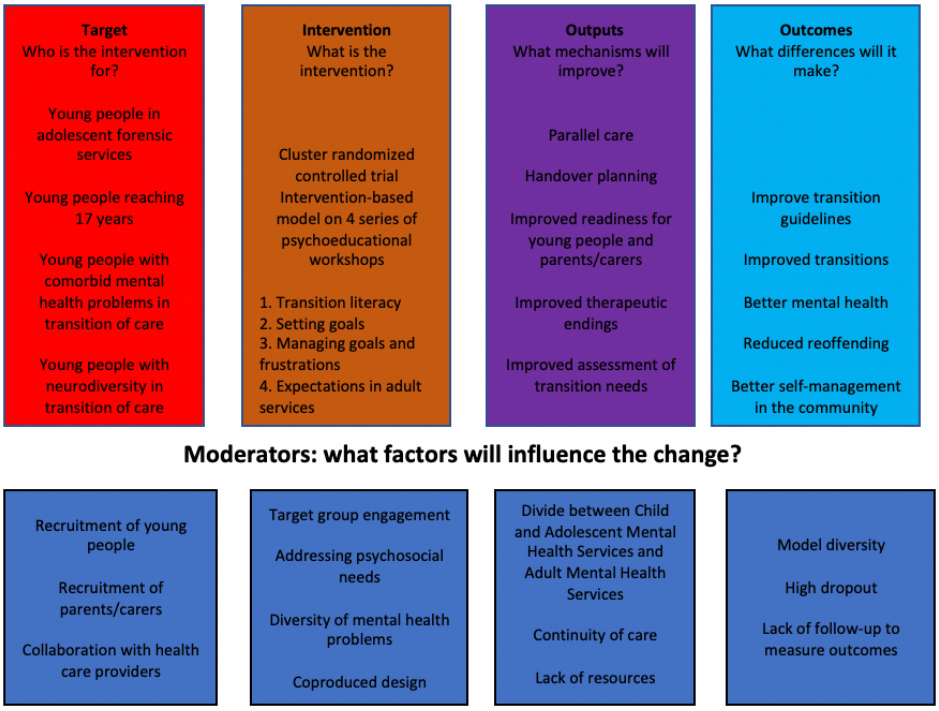
- Design a multicenter intervention for young people in transition;
- Design training manuals/toolkit for the health care staff involved in transition;
- Reflect on good practices across adolescent secure hospitals for transition to adult services and the community and management;
- Promote co-design and coproduction of evidence-based research.

The impact is as follows:

- Design of the future cRCT will promote effectiveness and cost-effectiveness;
- Assess barriers and facilitators to providing the proposed intervention;
- Help services to reflect on quality of care and performance pre- and postdischarge;
- Enable young people to voice their experiences and be dynamically involved in their care.

Figure 3 presents the outcomes for the full-scale trial.

Figure 3. Logic model: outcomes for the full-scale trial.



Discussion

Key Findings in Coproduction

This study aimed to describe the first and second stages of coproducing the MOVING FORWARD intervention. We collaborated with young people, parents/carers, and key workers from adolescent secure hospitals. In addition to addressing the gaps and concerns highlighted above, this research builds upon a previous NIHR Collaborations for Leadership in Applied Health Research and Care–funded PhD project titled *Transition of care in young offenders*, a multiphased study that illustrated

the need for a national integrative care model that acknowledges the complexities involved in young people's care journey. Factors found to impede effective transitions pertained to the severity of index offence, lack of parental involvement, disorganized service planning, and inconsistent clinical practice [20]. Groups at disadvantage were also highlighted, including young females with emerging borderline personality disorders and males with high-risk learning disabilities and long-term seclusion. Acknowledging the diversity in needs among young people has helped to coproduce and tailor the proposed intervention.

Patient and Public Involvement

Young people and parents/carers are central to this study. Young people in secure care present with multiple comorbidities and challenging behavior, and do not have a dynamic role in decision-making as a result of being detained under the Mental Health Act legislation. Parents/carers are particularly concerned about transitions as they do not know what to expect and do not feel involved in the process. PPI will be sought at all stages of the study to improve outcomes in design, data collection, analysis, and dissemination. External PPI members will receive relevant training during the early stages of the study, and a point of contact from each site will be identified to ensure emotional support is provided in the event the young people feel distressed and direct them to appropriate services. A total of 5 young people and 5 parents/carers will be recruited to represent the study's steering/PPI group and meet twice annually over the course of 4 years at St. George's Hospital. One NHS commissioner and 2 health care providers will be involved in the steering groups.

Engagement of young people has been sought during the development of the intervention. The youth and parent/carer steering group will review information sheets, consent forms, and outcome measures to check their appropriateness. During the end of the study's second and final year, young people from the advisory and steering groups will be asked to aid with the dissemination of the interim reports to their community and/or hospitals. The parent/carer advisory groups will be recruited from St Andrew's and Cygnet's Sheffield hospitals, and their views about the intervention model and how it can benefit young people will be collected. Feedback from all stakeholders will help to interpret the findings effectively and address how the intervention can fit future cohorts transitioning out adolescent secure services to facilitate the continuity of care.

Acknowledgments

The authors would like to thank all participating sites for their time, advice, and contributions, as well as all the young people and parents/carers who have shared their service transition experiences and provided valuable feedback and input for the proposed intervention.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavior therapy
CPA: Care Programme Approach
cRCT: cluster randomized controlled trial

EQ-5D-Y: EuroQol Five-Dimensional Questionnaire, Youth Version
ICC: intraclass correlation
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
NIHR: National Institute for Health Research
PARS-III: Personal Adjustment and Role Skills Scale
PICU: psychiatric intensive care unit
PPI: patient and public involvement
SLOF: Specific Levels of Functioning Scale
SST: social skills training
TAU: treatment as usual
TRAQ: Transition Readiness Assessment Questionnaire
TROM: Transition Related Outcome Measure
WHOQOL-BREF: World Health Organization Quality of Life Assessment

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Protocol

Surgery With Arterial Resection for Hilar Cholangiocarcinoma: Protocol for a Systematic Review and Meta-analysis

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Abstract

Background: In light of recent advances in multimodality treatment, an analysis of vascular resection outcomes in surgery for hilar cholangiocarcinoma is lacking.

Objective: The aim of this meta-analysis is to summarize the currently available evidence on outcomes of patients undergoing arterial resection for the treatment of hilar cholangiocarcinoma.

Methods: A systematic literature search in the databases PubMed/MEDLINE, Cochrane Library, and CINAHL, and the trial registries ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform will be carried out. Predefined outcomes are mortality (100-day and in-hospital), morbidity (Clavien-Dindo classification, any type of complication), vascular complications (thrombosis or stenosis of the portal vein or hepatic artery, pseudoaneurysms), liver failure, postoperative bleeding, duration of surgery, reoperation rate, length of hospital stay, survival time, actuarial survival (2-, 3-, and 5-year survival), complete/incomplete resection rates, histologic arterial invasion, and lymph node positivity (number of positive lymph nodes and lymph node ratio).

Results: Database searches will commence in December 2020. The meta-analysis will be completed by December 2021.

Conclusions: Our findings will enable us to present the current evidence on the feasibility, safety, and oncological effectiveness of surgery for hilar cholangiocarcinoma with arterial resection. Our data will support health care professionals and patients in their clinical decision-making.

Trial Registration: PROSPERO 223396; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=223396

International Registered Report Identifier (IRRID): DERR1-10.2196/31212

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KEYWORDS

meta-analysis; cholangiocarcinoma; arterial resection; surgery; vascular resections; cardiology; outcomes; mortality; morbidity; perioperative; cancer; tumor; liver; liver cancer

Introduction

Cholangiocarcinoma has an estimated incidence of 1 to 2 per 100,000 persons per year [1] and constitutes the second most common primary hepatic malignancy [2]. The effect of systemic treatment is limited in the majority of patients, and surgery with complete removal of the tumor is the only option offering a chance of cure or at least of long-term freedom from the tumor. In operated patients, a 20% to 30% 5-year overall survival can be achieved [3,4]. Most cholangiocarcinomas arise in the area of the bile duct bifurcation. They are commonly referred to as hilar cholangiocarcinoma or Klatskin tumor [5]. Due to the

proximity of vascular structures to the bile duct bifurcation, tumor invasion of the portal vein, the proper hepatic artery, or the contralateral hepatic artery (ie, a tumor arising from the left bile duct invading the right hepatic artery) occurs in a relevant proportion of cases.

Vascular and especially arterial resection and reconstruction during surgical removal of hilar cholangiocarcinoma is a debated issue. Although it is the only way of facilitating complete resection in case of vascular invasion, there are concerns of high postoperative morbidity and mortality following vascular reconstruction, including hemorrhage and liver failure, which might offset the survival advantage gained from complete tumor removal. However, thanks to technical improvements in microvascular anastomoses and to a growing experience with liver transplants in many centers, the surgical approaches for hilar cholangiocarcinoma have generally become more aggressive in recent years, and thus, the number of studies assessing feasibility, safety, and oncological effectiveness of arterial resection and reconstruction has grown [6-10].

To summarize the currently available evidence on the topic, we plan to conduct a systematic review with meta-analysis.

Methods

The literature search and data analysis will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [11]. The study has been registered in the PROSPERO database (ID 223396) [12].

Search Strategy

The databases PubMed/MEDLINE, Cochrane Library, CINAHL, and the trial registries ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform will be searched through their respective online search engines. The search will be performed on studies published between database inception and a defined search date. The search strategies used in the individual databases are displayed in Multimedia Appendix 1. Furthermore, the reference lists of the included studies will be manually searched to find relevant articles. Abstracts and full-text reviews will be evaluated independently in a standardized manner by two authors to assess eligibility for inclusion or exclusion. Disagreements between reviewers will be resolved by consensus; if no agreement can be reached, a third reviewer will decide whether to include the study.

Inclusion and Exclusion Criteria

Articles in the English, German, Spanish, Portuguese, and Italian language will be considered. Studies reporting resection of cholangiocarcinoma, both primary and secondary, in curative intention including resection of a segment of the hepatic artery with a control group of patients undergoing resection without arterial resection will be included. Review articles, case reports, case series with less than 5 patients, comments, and letters will not be included. The details of the study selection process will be summarized in a flowchart.

Data Collection

Data from the individual included studies will be extracted separately by two authors and collected in a dedicated database. The following descriptive data will be documented for each selected study: first author, year of publication, inclusion period of the study, country where the study was conducted, sample size, and mean or median follow-up time. The distribution of the following patient and operation characteristics will be documented: age, gender, American Society of Anesthesiologists classification, Eastern Cooperative Oncology Group performance status, preoperative chemotherapy (yes/no, regimen), type of operation, type of vessel resection and reconstruction, duration of surgery, and blood loss. The following predefined outcomes will be extracted:

- Mortality (100-day and in-hospital)
- Morbidity (any complication according to the Clavien-Dindo classification [13] or another classification used in the respective study)
- Vascular complications (thrombosis, stenosis, or pseudoaneurysm of the portal vein or hepatic artery)
- Liver failure (as defined in the respective study)
- Postoperative bleeding (as defined in the respective study)
- Reoperation rate
- Mean and median survival
- 1-, 2-, 3-, and 5-year survival rates
- Proportion of macroscopically complete (R0), microscopically incomplete (R1), and macroscopically incomplete (R2) resection, and of patients without any resection upon surgery
- Histopathological tumor stage (pTNM)
- Proportion of patients with histologically confirmed arterial tumor invasion
- Mean and median of tumor-positive lymph nodes and of retrieved lymph nodes

For each study, the risk of bias will be assessed using the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) tool suggested by the Cochrane Collaboration [14]. An ideal randomized controlled trial on the pertinent research question will be conceived and emulated. The actual studies included in the meta-analysis will be compared with this emulated trial regarding their risk of bias in the following domains:

- Preintervention domains
  - Bias due to confounding
  - Bias in selection of participants into the study
- Intervention domain
  - Bias in classification of interventions
- Postintervention domains
  - Bias due to deviations from intended interventions
  - Bias due to missing data
  - Bias in measurement of the outcome
  - Bias in selection of the reported result

For each domain, the tool foresees *signaling questions* whose response options are yes, probably yes, probably no, no, and no information. Based on the responses, the risk of bias for each

domain will be judged as low, moderate, serious, critical, or no information. From the risk of bias for the single domains, an overall risk of bias for the study will be ascertained according to Table 1.

Because it is not expected that any randomized controlled trials will be identified for inclusion into the meta-analysis, no specific risk of bias assessment for such trials is planned.

Table 1. Bias judgement [14].

Overall risk of bias judgement	Interpretation	Criterion
Low risk of bias	The study is comparable to a well-performed randomized trial.	The study is judged to be at low risk of bias for all domains for this result.
Moderate risk of bias	The study appears to provide sound evidence for a nonrandomized study but cannot be considered comparable to a well-performed randomized trial.	The study is judged to be at low or moderate risk of bias for all domains.
Serious risk of bias	The study has one or more important problems.	The study is judged to be at serious risk of bias in at least one domain but not at critical risk of bias in any domain.

Statistical Analysis

A meta-analysis with the following outcomes will be performed:

- Morbidity (any complication according to the Clavien-Dindo classification [13] or another classification used in the respective study)
- Vascular complications (thrombosis, stenosis, or pseudoaneurysm of the portal vein or hepatic artery)
- Liver failure (as defined in the respective study)
- Postoperative bleeding (as defined in the respective study)
- Reoperation rate
- 1-, 2-, 3-, and 5-year survival rates
- Proportion of macroscopically complete (R0), microscopically incomplete (R1), and macroscopically incomplete (R2) resection, and of patients without any resection upon surgery
- Histopathological tumor stage (pTNM)
- Proportion of patients with histologically confirmed arterial tumor invasion
- Mean and median of tumor-positive lymph nodes and of retrieved lymph nodes

The Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration) will be used. The magnitude of the effect estimate will be visualized by forest plots. An odds ratio will be calculated for binary data and the weighted mean difference and relative difference of SD for continuous data. The 95% CI, heterogeneity, and statistical significance will be reported for each outcome. The chi-square and Kruskal-Wallis tests will be used for the evaluation of statistical significance. $P<.05$ will be considered statistically significant. When the studies do not report mean and SD, these will be calculated using the methods described by the guidelines of the Cochrane Collaboration [15] and Hozo et al [16]. As not all studies report hazard ratios, the survival analysis will be performed with weighted rates at the predefined time points previously listed. The outcome postoperative complications will be dichotomized (grade 1 and 2 vs grade 3a and higher according to the Clavien-Dindo classification). The incidence of severe complications (grade 3a and higher) per group will be determined and compared using the chi-square test and a forest plot. The histopathological tumor stage (pTNM) will be qualitatively described for the groups.

Subgroup analysis for patients with portal vein resection and patients who had undergone neoadjuvant chemotherapy prior to resection will be performed.

Sensitivity analyses will be conducted according to ascertained risk of bias as previously described. For these, all studies with a high/serious risk of bias will be excluded, and the analyses of the outcomes, as previously described, will be conducted.

Results

Database searches will commence in December 2020. The meta-analysis will be completed by December 2021.

Discussion

This systematic review with meta-analysis will synthetize all available evidence on feasibility, safety, and oncological effectiveness of arterial resection and reconstruction during surgical removal of hilar cholangiocarcinoma. It will be conducted according to the defined protocol presented here and will be reported following the recommendations stipulated in the PRISMA statement, thus ensuring the highest quality standards and minimizing the risk of possible bias [11]. The expected results will support health care professionals and patients with locally advanced hilar cholangiocarcinoma in their decision making. Specifically, we expect the results to show if concerns of high postoperative morbidity and mortality following vascular reconstruction, which might offset the survival advantage gained from complete removal of the tumor, are indeed justified.

Authors' Contributions

AR outlined, wrote, and drafted the manuscript. All authors critically revised the manuscript and read and approved the final version of the manuscript.

Conflicts of Interest

None declared

Multimedia Appendix 1
Search strategy.
[DOCX File , 31 KB - resprot_v10i10e31212_app1.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions

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Protocol

Four Decades of Military Posttraumatic Stress: Protocol for a Meta-analysis and Systematic Review of Treatment Approaches and Efficacy

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Abstract

Background: Over 85% of active members of the Canadian Armed Forces have been exposed to potentially traumatic events linked to the development of posttraumatic stress disorder (PTSD). At the time of transition to civilian life, as high as 1 in 8 veterans may be diagnosed with PTSD. Given the high prevalence of PTSD in military and veteran populations, the provision of effective treatment considering their unique challenges and experiences is critical for mental health support and the well-being of these populations.

Objective: This paper presents the protocol for a meta-analysis and systematic review that will examine the effectiveness of treatment approaches for military-related PTSD.

Methods: This PROSPERO-preregistered meta-analysis is being conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane guidelines. A comprehensive search of the literature was

conducted using the databases PsycInfo, Medline, Embase, CINAHL, and ProQuest Dissertation & Theses. Effect sizes will be computed based on changes in PTSD symptom scores over time across studies using validated PTSD scales. A multilevel meta-analysis will examine the overall effects, between-study effects, and within-study effects of available evidence for PTSD treatments in military populations. Effect sizes will be compared between pharmacotherapeutic, psychotherapeutic, and alternative/emerging treatment interventions. Finally, meta-regression and subgroup analyses will explore the moderating roles of clinical characteristics (eg, PTSD symptom clusters), treatment approaches (eg, therapeutic orientations in psychotherapy and alternative therapies and classifications of drugs in pharmacotherapy), as well as treatment characteristics (eg, length of intervention) on treatment outcomes.

Results: The literature search was completed on April 14, 2021. After the removal of duplicates, a total of 12,002 studies were screened for inclusion. As of July 2021, title and abstract screening has been completed, with 1469 out of 12,002 (12.23%) studies included for full-text review. Full review is expected to be completed in the summer of 2021, with initial results expected for publication by early winter of 2021.

Conclusions: This meta-analysis will provide information on the current state of evidence on the efficacy and effectiveness of various treatment approaches for military-related PTSD and identify factors that may influence treatment outcomes. The results will inform clinical decision-making for service providers and service users. Finally, the findings will provide insights into future treatment development and practice recommendations to better support the well-being of military and veteran populations.

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KEYWORDS

military personnel; psychotherapy; pharmacotherapy; stress disorders; posttraumatic; meta-analysis; systematic review; therapy; stress; disorder; posttraumatic stress disorder; review; treatment; efficacy; military; Canada; veteran

Introduction

Background

Over 85% of active members of the Canadian Armed Forces have reported exposure to potentially traumatic events [1], and studies estimate that between 7.5% and 12.9% of veterans are diagnosed with posttraumatic stress disorder (PTSD) on return to civilian life [2,3]. Military-related PTSD may differ from PTSD experienced by civilians [4]. The risk factors, etiology, and prognosis of military-related PTSD are associated with military service, deployment stressors, and unique potentially traumatic events. These events include experiences of combat, moral injury, military sexual trauma, and the LGBTQ Purge [2,5,6]. As a result, PTSD treatment for military and veteran populations may differ in effectiveness from that for nonmilitary populations. Studies have shown that outcomes of both pharmacotherapy and psychotherapy for military-related PTSD have a smaller effect size than those for civilian-related PTSD; military members and veterans have reported poorer response to treatments than civilians [7-9]. In a recent review, Coventry et al [10] noted that while trauma-focused therapies were particularly effective in treating PTSD, the effect was less for military- and veteran-related PTSD.

Given the prevalence of PTSD and the uniqueness of the PTSD experience in military populations, the provision of effective treatment and support is of utmost importance. However, ambiguities and heterogeneities in reports of effectiveness are challenging for service providers [11]. Recent reviews highlight the lack of consensus regarding the trajectory of PTSD, the diversity of approaches in the diagnosis and treatment of PTSD, and the inconsistencies in defining response to PTSD treatments as problematic [10,12-14]. In addition, novel empirical evidence has also underscored service users participating in the treatment decision-making process as additional important determinants of treatment outcomes [4]. Provision of timely, appropriate, and effective treatments and support that are aligned across organizations, service providers, and service users is critical to the well-being of military personnel and veterans. Thus, we aim to provide an overview of the effectiveness of existing treatment options for military-related PTSD.

Treating Military-Related PTSD

Since the classification of PTSD as a mental disorder in 1980, treatments have evolved to encompass a diversity of approaches, targeting a multitude of symptomology, functioning, and pathways. As a result, clinicians and mental health service providers face the difficult challenge of developing a treatment plan for those diagnosed with PTSD. Current evidence-based treatments can be classified into two categories: psychologically based and pharmacologically based treatments.

The majority of the empirically supported psychological treatments for PTSD fall within the cognitive behavioral therapy framework. Examples of these treatments include cognitive processing therapy [15], trauma-focused cognitive behavioral therapy [16], and prolonged exposure [17]. Outside of the cognitive behavioral therapy framework, another empirically supported treatment for PTSD is eye movement desensitization and reprocessing [18]. In the military context, trauma-focused psychotherapies (prolonged exposure, cognitive processing therapy, and eye movement desensitization and reprocessing) are the most recommended approaches to treating PTSD [19]. These therapies focus on trauma-related negative cognitions and challenging situational and cognitive avoidance as well as on processing the meaning of the trauma. Together, prolonged exposure, cognitive processing therapy, and eye movement

desensitization and reprocessing have shown to be most effective in ameliorating PTSD symptoms [19,20]. While much of the effectiveness of these treatments has been evaluated in individual therapy format, there is also increasing empirical support for administering these treatments—specifically cognitive processing therapy—in group format [21]. Some recent studies have also found selective interventions to be noninferior to some trauma-focused therapies, including interpersonal psychotherapy [22] and acceptance and commitment therapy [23].

Pharmacological treatment of PTSD involves the use of various psychotropic medications to target the core symptoms of PTSD, including intrusions, avoidance, negative alterations in cognition and mood, and alteration in arousal and reactivity [24]. As of July 2021, typical pharmacotherapies to treat PTSD include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, atypical antipsychotics, β-blockers, and sleep medications (eg, α-blockers, nabilone, hypnotics) [24]. Pharmacological treatments can be categorized by medication typologies, including antidepressants (eg, sertraline), antipsychotics (eg, risperidone), anticonvulsants (eg, topiramate), hypnotics (eg, zopiclone), and mood stabilizers (eg, lithium). In addition to classification according to drug typology, pharmacotherapy treatments can also be categorized by mechanisms of action.

Besides psychological and pharmacological treatments, there are a number of alternative and emerging treatments targeting different aspects of PTSD symptomology. These can include clinical treatments such as deep brain stimulation [25], noninvasive brain stimulation via repetitive transcranial magnetic stimulation, transcranial direct current stimulation [26], and neurofeedback [27]. Emerging therapies may also include cognitive-based conjoint therapy for PTSD [28], animal-assisted therapy [29], and yoga or mindfulness-based therapies [30]. In addition, given the high rates of comorbidities in individuals with PTSD, many approaches have incorporated the treatment of comorbidities to create new combination or adjunctive therapies for the treatment of PTSD [31]. These can include medication-enhanced psychotherapies such as methylenedioxymethamphetamine [32] and virtual reality–based treatments [33].

Determinants of Treatment Approaches and Clinical Outcomes

A number of review studies have summarized the effectiveness of various treatment approaches. A head-to-head review comparing psychological and pharmacological treatments of combat-related PTSD in 25 studies found that pharmacotherapeutic approaches were slightly more efficacious than psychotherapeutic approaches in ameliorating PTSD symptoms [34]. A network meta-analysis of treatments for PTSD and other mental health conditions stemming from complex trauma drew a contrasting conclusion from the results of 116 studies [10]. The findings suggested that pharmacological interventions were less effective than psychological interventions in the treatment of PTSD and associated functions such as sleep [10]. In addition to disparities across review findings, questions arise, including which factors, if any, influence the effectiveness of various treatment approaches, for whom are different interventions most effective, and what contextual factors, if any, can bolster the effectiveness of treatment approaches for this unique population.

Furthermore, additional effort is needed to expand the scope of reviews. Many reviews included evidence exclusively from randomized controlled trials that often used monotherapies or exclusion criteria [35]. However, the clear-cut criteria applied in research share little overlap with the complexities of real-life practices and experiences of diagnosing and treating PTSD in military and veteran populations. Treatment providers contend with complexities of patient characteristics (eg, chronicity and type of trauma), clinical characteristics of PTSD (eg, symptom clusters, prior treatment or use of medications, and comorbidities), and treatment characteristics (eg, length of treatment, type of treatment and augmentation [13], add-on, and adjunctive treatments) when making treatment-related decisions. In addition, treatment planning is often conducted with patient engagement and feedback in mind [36], and may involve many parallel processes with different health and mental health providers.

Aims and Objectives

Through a multilevel meta-analytic model, this meta-analysis and systematic review will review the state of evidence on existing treatment options for military-related PTSD and their effectiveness via a preregistered meta-analysis and systematic review. The meta-analysis will serve as a comprehensive scan of the literature while discriminating between effective and ineffective approaches based on considerations of clinical characteristics, treatment characteristics, and individual differences. The systematic review will evaluate the quality of the evidence and examine treatment fidelity, study rigor, and certainty of evidence. Protocols for the meta-analysis and systematic review were developed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and preregistered on PROSPERO to ensure transparency and replicability [37].

Methods

Search Strategy

The literature search was conducted using multiple databases (PsycINFO, PubMed/Medline, Embase, CINAHL, and ProQuest Dissertation & Theses) on April 14, 2021, with a date restriction of 1980. The date restriction represents the first issue of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) *III*, in which PTSD was officially defined as a distinct diagnosis. In addition to these exploratory databases, we also used PTSDpubs, the JBI Database of Systematic Reviews and Implementation Report, and the Cochrane Library; hand searched for relevant articles via bibliographies; and used known author contact to search for additional titles for potential inclusion.

Eligibility Criteria

The following criteria were considered for inclusion in the study: (1) adults; (2) military personnel or veterans; (3) individuals with a current diagnosis of PTSD—with etiology due to military

service (eg, combat-related PTSD)—under DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, or International Classification of Diseases criteria; (4) those with some form of incorporated treatment (psychotherapy, pharmacotherapy, alternatives); and (5) those in whom PTSD symptom change was measured via validated measures of PTSD severity (eg, PTSD Checklist for DSM-5). Exclusion criteria were (1) reviews and meta-analyses (though used for known author contact and search); (2) studies with nonadult populations (eg, children, nonhuman); (3) case studies with sample sizes of less than 5; (4) studies without a primary or secondary focus on PTSD in military and veteran populations; and (5) studies with no quantitative data (eg, protocols, corrections, commentaries, and qualitative studies).

Comparison Groups

While the overall effects of treatments for PTSD will be aggregated and analyzed, the current meta-analysis and systematic review will mainly explore heterogeneities in treatment approaches. These approaches can be broadly categorized as psychological treatments, pharmacological treatments, and alternative/emerging treatments. Psychological treatment is defined as any intervention grounded in the treatment of mental health through individual psychotherapy and delivered by registered mental health professionals. Pharmacological treatments are defined as any therapeutic approaches using prescribed medication(s) as the primary method of treatment. Alternative and emerging treatments include any alternatives and emerging treatments falling outside of the psychological and pharmacological treatment approaches (eg, equine therapy, deep brain stimulation, and ketamine-assisted therapy).

Measures of Outcomes and Effect

This review will assess changes in PTSD as measured from baseline to postintervention (psychotherapy, pharmacotherapy, or alternative/emerging treatment modality) using validated psychometric scales of PTSD. Measurements taken will report continuous values of PTSD symptomatology and can include the Clinician-Administered PTSD Scale for DSM-5 [38]; the PTSD Checklist for Military and Civilians for DSM-IV [39]; the PTSD Checklist for DSM-5 [40]; the Primary Care PTSD Screen for DSM-5 [41]; the Dissociative Subtype of PTSD Scale [42]; the Posttraumatic Diagnostic Scale for DSM-5 [43]; and the PTSD Symptom Scale [44].

Intervention effects will be examined using mean differences captured via continuous data, and aggregate data will be represented as Hedges *g*, calculated by the differences in means divided by the weighted pooled SD [45]. Hedges *g* combines the SDs of experimental and control groups, resulting in single SD estimates of group differences [46]. Effect sizes will be interpreted based on the recommendation made by Ferguson [46]: Hedges *g* of 0.41 for a minimum effect size representing a practically significant effect in social science, 1.15 for a moderate effect, and 2.70 for a strong effect. In addition to changes in PTSD symptomatology, secondary outcomes will include functional changes related to PTSD, such as quality of life, cognition, and sleep quality, as well as symptoms of commonly reported diagnostic comorbidities of PTSD like major depressive disorder and anxiety disorders.

Study Identification and Selection

Independent raters will be trained to evaluate studies against eligibility criteria. Studies will be included if they contain continuous PTSD evaluation data collected at the pre- and postintervention stages via validated measures. For the pharmacotherapy group, selection will include a baseline assessment of symptom severity for evaluation of treatment effectiveness followed by the administration of a psychotropic medication. For the psychotherapy group, selection will include a baseline evaluation followed by the administration of a psychologically based treatment. Study reviews are conducted on SWIFT-Active Screener (Sciome), a web-based collaborative screening software for systematic reviews [47]. The reviews will be completed by 8 raters (TL, AB, KS, YL, IK, JS, BJ, and EK). Any disagreements will be resolved through group discussion to reach mutual consensus, led by the first author.

Data Extraction

From each study, the following data will be extracted: sample size; means and SDs of PTSD scores pre- and post- or mean difference and *P* values; means and SDs of secondary outcome scores pre- and post or mean difference and *P* value (if available); pre- and postcorrelations; type of intervention; moderator variables (if available); clinical characteristics; treatment characteristics; and study characteristics.

Missing data will be handled through author contact. A designated member of the research team will email the corresponding authors or research leads for missing data. A follow-up email will be sent after 1 week over a 2-week response window. All data extracted and received will be recorded via Smartsheet (Smartsheet Inc) and exported to R (R Foundation for Statistical Computing) and Comprehensive Meta-Analysis software (Biostat Inc) for data analysis.

Strategy for Data Synthesis and Meta-analyses

Using Cochrane's guide as a framework for data synthesis, the proposed meta-analysis will seek a minimum of 15 studies to be included for overall analysis, and a minimum of 4 studies to be included for subgroup analyses. For each study, pre- and postintervention means and SDs, along with sample size, will be used to calculate effect sizes. Pre- and postintervention correlations will be calculated based on known data and entered for analysis. For studies without pre- and postintervention data, differences between means, paired-group *P* values, and directions of effects found will be used as alternative methods to calculate effect sizes. Data will be analyzed using Comprehensive Meta-Analysis software [48] and the *metafor* R package [49].

The main analyses of the meta-analysis will comprise a multilevel meta-analytic approach to examine dependency among effect sizes of studies, including overall effects, between-study effects, and within-study effects. Overall analysis will compare group-aggregated effects of psychotherapy with group-aggregated effects of pharmacotherapy. Subgroup analysis will be used to examine the moderating role of clinical

characteristics (eg, presence and absence of comorbid disorders, PTSD symptom clusters, trauma exposure type, and lifetime diagnosis), treatment characteristics (eg, treatment approach, length, fidelity, and study rigor), and study characteristics (eg, participant demographics, PTSD measurements used, and operationalizations of PTSD). Finally, publication bias will be explored via the visual inspection of funnel plots, the 3-level Egger regression test, the trim-and-fill method, and Orwin fail-safe N.

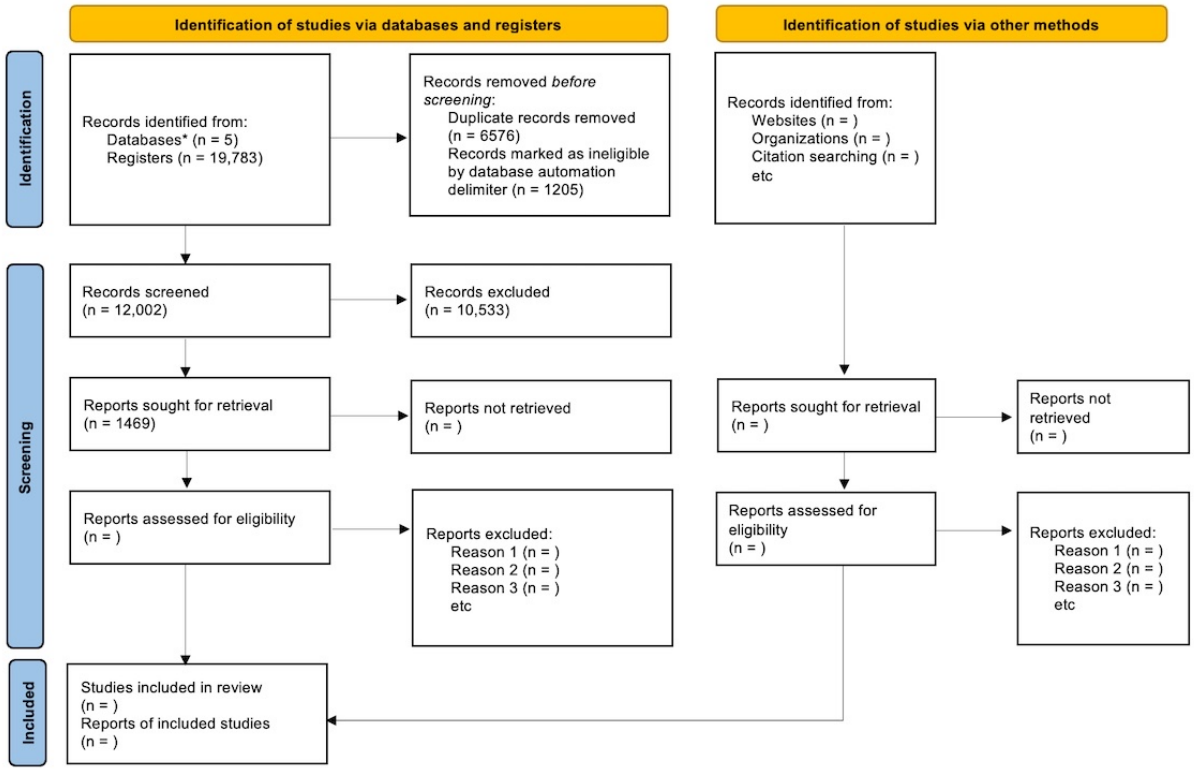
Systematic Review and Risk-of-Bias (Quality) Assessment

The systematic review portion of the proposed review will examine intervention fidelity and study rigor. Methods of quality assessment will take into consideration both the quality of studies reported as well as the fidelity of intervention design and delivery. Assessment of fidelity will follow existing frameworks and include benchmarks of design, delivery, receipt, and enactment [50]. Assessment of study rigor will include benchmarks of research design, participant selection, and appropriateness of statistical analysis. Finally, Cochrane's guide to GRADE (Grading of Recommendations, Assessment, Development and Evaluations) assessment will be applied to evaluate the certainty of evidence found within the proposed meta-analysis [51].

Results

The literature search was completed on April 14, 2021. Following the removal of duplicates using the *synthesisr* R package, 12,002 articles were retained for initial title and abstract review. As of July 2021, title and abstract screening has been completed, with 1469 out of 12,002 (12.23%) studies included for full-text review. The PRISMA flow diagram is shown in Figure 1 [52]. Initial interrater reliability for the title and abstract review was 93.7% (761/12,002 conflicts, 6.34%). Full review is expected to be completed in the summer of 2021, with initial results expected for publication by early winter of 2021.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. *PsycINFO-OVID (n=5050); MEDLINE-OVID (n=3978); EMBASE-OVID (n=5631); CINAHL (n=5033); ProQuest Dissertation & Theses (n=91).



Discussion

This paper describes the protocol for a meta-analysis and systematic review of the literature on the effectiveness of existing treatment approaches for military-related PTSD. The review will address gaps in the literature, including complexities of the clinical characteristics of PTSD, approaches of and diversities in implementing treatments, and population characteristics that may influence treatment outcomes. This comprehensive review aims to broadly substantiate evidence of PTSD treatment effectiveness to advance consensus guidelines for the treatment of military-related PTSD. The outcomes of this review will serve as a database of available evidence on the treatment of PTSD in military and veteran populations and begin to examine unanswered questions related to treating military-related PTSD.

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Conflicts of Interest

None declared.

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Abbreviations

DSM: Diagnostic and Statistical Manual of Mental Disorders
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD: posttraumatic stress disorder

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Protocol

Assessing the Real-time Influence of Racism-Related Stress and Suicidality Among Black Men: Protocol for an Ecological Momentary Assessment Study

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Abstract

Background: Suicide is the third leading cause of death among Black adults aged 18-35 years. Although men represent a majority of suicide deaths among Black adults, less is known regarding the extent to which unique cultural stressors, such as racism-related stress (eg, racial discrimination), are salient in exacerbating suicide risk among Black men. Moreover, few studies examine the daily influence of racism-related stressors on suicide outcomes using real-time smartphone-based approaches. Smartphone-based mobile health approaches using ecological momentary assessments (EMA) provide an opportunity to assess and characterize racism-related stressors as a culturally sensitive suicide risk factor among Black young adult men.

Objective: The goal of this study is to describe a protocol development process that aims to capture real-time racism-related stressors and suicide outcomes using a smartphone-based EMA platform (MetricWire).

Methods: Guided by the Interpersonal Theory of Suicide (ITS), we developed a brief EMA protocol using a multiphased approach. First, we conducted a literature review to identify brief measures previously used in EMA studies, with special emphasis on studies including Black participants. The identified measures were then shortened to items with the highest construct validity (eg, factor loadings) and revised to reflect momentary or daily frequency. Feasibility and acceptability of the study protocol will be assessed using self-report survey and qualitative responses. To protect participants from harm, a three-tier safety protocol was developed to identify participants with moderate, elevated, and acute risk based on EMA survey response to trigger outreach by the study coordinator.

Results: The final EMA protocol, which will be completed over a 7-day period, is comprised of 15 questions administered 4 times per day and a daily questionnaire of 22 items related to sleep-related impairment and disruption, as well as racism-related stress. Study recruitment is currently underway. We anticipate the study will be completed in February 2023. Dissemination will be conducted through peer-reviewed publications and conference presentations.

Conclusions: This protocol will address gaps in our understanding of Black men's suicide outcomes in the social contexts that they regularly navigate and will clarify the temporal role of racism-related stressors that influence suicidal outcomes.

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KEYWORDS

Black men; suicide; racism; ecological momentary assessment

Introduction

In recent years, suicide completion rates among Black Americans have increased significantly [1-4]. According to the Centers for Disease Control and Prevention, in 2018, suicide emerged as the third-leading cause of death among Black adults aged 18-35 years [5]. Among Black suicide decedents, men comprise the majority (81%) [5]. In response to rising rates of suicide completion, researchers and policy makers have identified the timely recognition and mitigation of suicide risk factors among Black young adult individuals as an emerging public health priority [3,4,6]. Although previous research has identified potential therapeutic approaches for Black males at risk of suicide [7], few studies have identified distinguishable risk factors occurring in Black men's daily social environment that may exacerbate suicidal thoughts and behaviors. To address this knowledge gap, cultural factors that affect the lived experience of Black men warrant further exploration.

Scholars assert that, among Black Americans, racial discrimination is a chronic stressor that may be more likely to result in a lower quality of life and higher psychological distress compared to their White counterparts [8-10]. Previous studies show that racism-related stressors are directly linked to poorer mental health outcomes, and are also specifically associated with fatal and nonfatal suicide outcomes in Black populations [11,12]. Goodwill and colleagues [10] found that, when compared to other sources of everyday discrimination (eg, generalized or attributed to other marginalized status such as gender or age), everyday race-based discrimination was the only type of discrimination that was significantly associated with increased rates of depressive symptoms and suicidal ideation. Although past studies examined frequent exposure to racial discrimination and its association with suicidal behaviors, authors of these studies suggest that this stressor operates dynamically over time as a function of the social environment that Black men regularly navigate. Indeed, racism is embedded in our society such that it creates dynamic subsystems that constantly reinforce one another [11,12], and thus cannot be captured at a single time point using a cross-sectional design alone. Thus, methodological approaches for examining dynamic shifts in racism-related stress exposures and suicide outcomes are needed.

The Interpersonal Theory of Suicide (ITS), developed by Thomas Joiner [13,14], has been a frequently applied framework to understand the proximal risk factors that precede suicidal behavior. This theory proposes that suicidal desire manifests from two interpersonal constructs—thwarted belongingness and perceived burdensomeness—with both being mediated by hopelessness. Additionally, ITS posits that the capability to engage in suicidal behavior is distinct from the desire to engage in that behavior [14]. To date, this model has not been applied extensively to Black men and does not adequately incorporate racism-related stressors as a potential mechanism in this behavioral process. One recent study applying the ITS model among African Americans found that hope moderated the relationship between thwarted belongingness and suicidal ideation [15]. Another study highlighted the relationship between racism and hopelessness and found that daily racial discrimination resulted in increased hopelessness among Black participants compared to other participants of varied racial and ethnic backgrounds that experience feelings of hopelessness [16]. Collectively, these studies identify racial discrimination as a unique antecedent to key risk factors related to suicide among Black Americans. Guided by these extant studies, additional research is needed to further test these explanatory mechanisms through more robust methodological designs that capture the dynamic, real-time, and longitudinal nature of racism-related stressors in the suicide experience.

Ecological momentary assessment (EMA) can be used to assess health information in real time, making this an effective approach to assess dynamic phenomena such as racism-related stressors. EMAs are used to repeatedly assess a sample's dynamic changes in behavior and experience in real time [17,18]. EMA approaches are useful for this research as they can be accessed conveniently through smartphones, which broadens the scope of this approach's applicability compared to paper-and-pencil or computer-assisted surveys. EMA also has noted advantages compared to other cross-sectional and longitudinal methods, such as minimizing recall bias and obtaining more accurate data, as these assessments are conducted in the subject's natural environment where they would feel most comfortable [17,18].

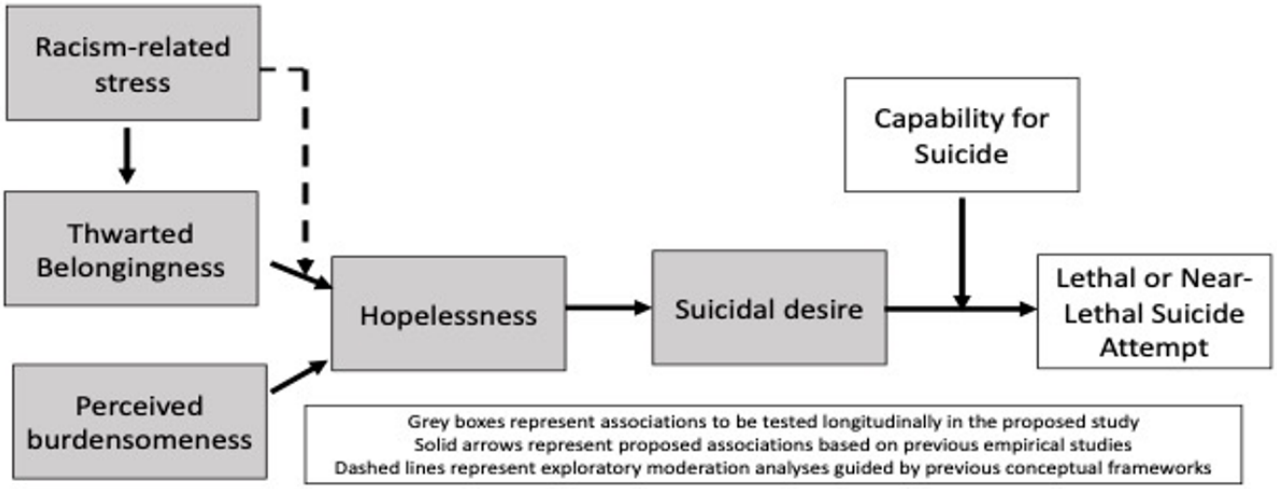
Despite technological advances in smartphone-based research and EMA studies, few studies have extended this approach to assess suicide outcomes in historically racialized populations such as Black men. To address these evidence gaps, the goal of our study is to develop a theory-informed EMA protocol for suitable use with a psychiatric sample of Black men aged 18-35 years. By integrating EMAs and smartphone technology, our findings will allow researchers to further understand how racism-related stressors may play a role in young Black men's daily life experiences and suicidal ideation and behaviors. Findings from this study will extend our understanding of the time-varying role of racism-related stressors beyond extant cross-sectional research and assess proximal factors of suicidal thought and behavior in real time.

Methods

Project Overview

The EMA study is part of a 2-year mixed methods investigation of the relationship between racism-related stress and suicidal thoughts and behaviors among Black young adult men aged 18-35 years. The larger study employs an exploratory sequential mixed methods design to adequately explore the phenomenon of rising suicide rates among Black men and integrate qualitative themes into more robust quantitative data collection processes in our EMA study at later phases [19]. In this study, we present our a priori EMA protocol development aimed at evaluating real-time assessments of suicidology among Black men. Eligible participants will complete a 7-day EMA procedure, whereby they self-report momentary suicidal thoughts and behaviors and proximal risk factors derived from our adapted ITS framework (Figure 1) using a smartphone-based app. We will also assess everyday experiences of racism-related stress and sleep patterns.

Figure 1. Adapted conceptual framework guided by Interpersonal Theory of Suicide.



Target Population and Eligibility

Eligible participants will meet the following inclusion criteria: (1) be aged 18-35 years; (2) identify as Black or African American; (3) have a past history of suicidal thoughts or behavior; (4) be able to speak, read, and understand English sufficiently well to complete the procedures of the study; (5) have a smartphone; and (6) have an outpatient mental health provider. We will exclude those who have been diagnosed with an active psychotic disorder, those with cognitive deficits or a medical condition that precludes full understanding of study materials, and those who are currently incarcerated.

Sample Size and Recruitment Procedures

Our intended study sample for this pilot study is 50 participants, which will yield initial feasibility data for the recruitment and retention approach of our study protocol for future scalable projects. The sample size was derived from previous EMA studies focused on suicide assessment in psychiatric populations [20-22]. For this sample size and study duration, we conservatively anticipate an 80% compliance rate, defined as completion of 23 surveys over the 7-day period.

We will identify eligible participants using two purposive sampling approaches. First, we will elicit direct referrals from Johns Hopkins Hospital outpatient psychiatrists, psychiatric nurses, and clinical social workers treating patients who fit the eligibility criteria. Additionally, we will use a clinical research recruiting service (sponsored by the Johns Hopkins Institute for Clinical and Translational Research) that identifies eligible participants in EPIC electronic health record databases. We will then provide recruitment information to active patients via MyChart, a web-based patient portal that provides patients with their personal health information and medical history and allows for communication between the patient and their health care provider or health care system. Eligible participants from both recruitment approaches will be referred to contact the study coordinator, who will then verify eligibility using an online screening survey. Once eligibility is confirmed, the coordinator will schedule a brief telephone discussion with the participant to provide additional information regarding the study and initiate the informed consent and enrollment process via REDCap.

Baseline Survey

Enrolled participants will be asked to complete a brief baseline assessment via REDCap. The survey will assess demographic characteristics, such as sexual orientation, education, and socioeconomic status. We will also include validated psychosocial measures associated with affective, gender, and race-specific factors associated with suicidal thoughts and behaviors, such as anger, sadness, attributional style, and racial identity. A complete list of baseline measures is presented in Table 1. Following completion, participants will receive a 15-minute overview of the MetricWire smartphone app and EMA questions via phone or Zoom call with the study coordinator. During this time, the study coordinator will schedule prompt times during regular waking hours (eg, 8AM to 10PM), schedule a follow-up time for the participant's exit interview, and record the contact information of the participant's outpatient mental health provider, when available, to implement into our safety protocol.

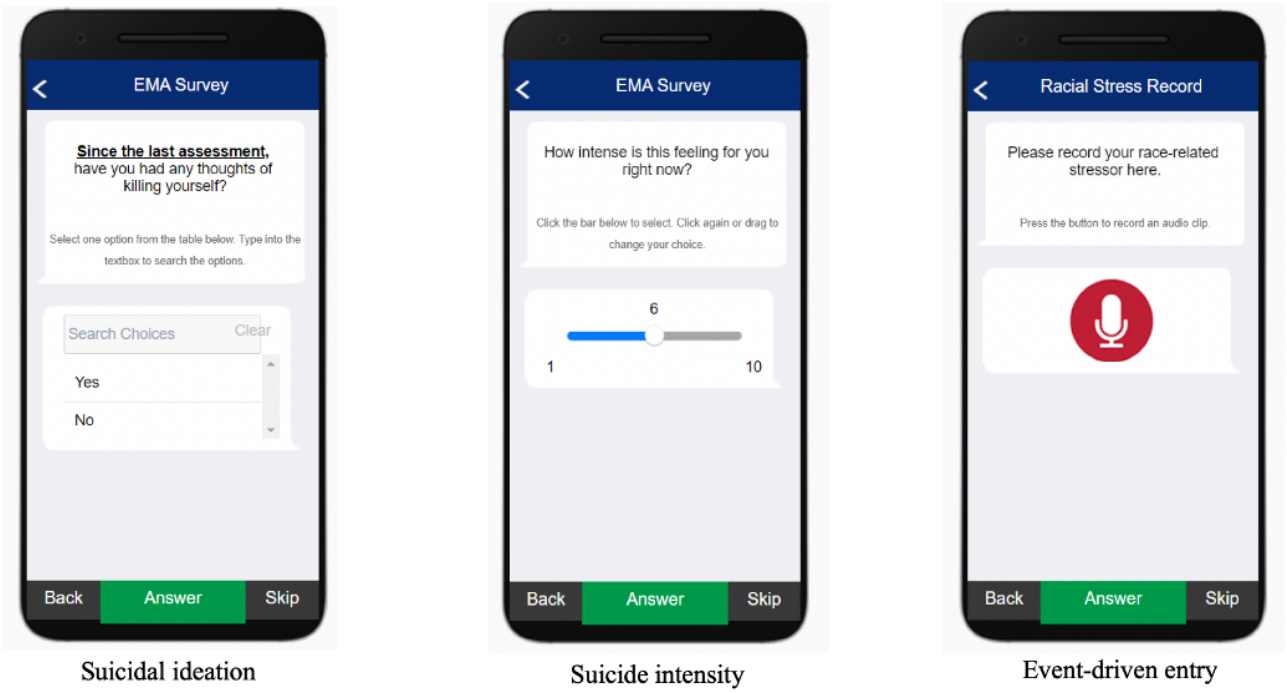
Table 1. Overview of baseline, ecological momentary assessment, and daily diary survey measures.

Variable	Baseline	Ecological momentary assessment (4 times per day)	Daily diary (once per day)
Age	✓		
Sexual orientation	✓		
Marital status	✓		
Employment status	✓		
Education status	✓		
Racial identity (Multidimensional Inventory of Black Identity [MIBI]) [23]	✓		
Anger (Dimensions of Anger Reactions-5 item [DAR-5]) [24]	✓		
Affective emotional states (Positive Affect and Negative Affect Schedule-Expanded Form [PANAS-X]) [25]	✓		
Emotional regulation (Emotional Regulation Questionnaire [ERQ]) [26]	✓		
Generalized social anxiety (Mini Social Phobia Inventory [Mini-SPIN]) [27]	✓		
Happiness (Pemberton Happiness Index [PHI]) [28]	✓		
Callousness (Inventory of Callous-Unemotional Traits [ICU]) [29]	✓		
Grit-S scale [30]	✓		
Psychache [31]	✓		
Suicidal thoughts and behavior (Columbia Suicide and Severity Rating Scale [C-SSRS]) [32]	✓	✓	
Hopelessness (Beck Hopelessness Scale [BHS]) [33]		✓	
Major depressive disorder (Patient Health Questionnaire-2 item [PHQ-2]) [34]		✓	
Perceived burdensomeness (Interpersonal Needs Questionnaire-Perceived Burdensomeness Subscale [INQ-PB]) [35]		✓	
Racism-related stress (Everyday Discrimination Scale [EDS]) [9]			✓
Capability of suicide (Acquired Capability for Suicide Scale [ACSS]) [36]		✓	
Thwarted belonginess (Interpersonal Needs Questionnaire-Thwarted Belongingness Subscale [INQ-TB]) [35]		✓	
Sleep-related impairment (Patient-Reported Outcomes Measurement Information System [PROMIS]) [37]			✓
Sleep disturbance (Patient-Reported Outcomes Measurement Information System [PROMIS]) [37]			✓

Data Collection Procedures

After completion of the baseline survey, participants will be asked to download the MetricWire app onto their personal smartphone for the study duration. The MetricWire app is available for both iOS and Android smartphone platforms at no cost in the Apple App Store or Google Play Store, respectively. Examples of the user interface of the MetricWire app are presented in Figure 2.

Figure 2. Select screenshots from the EMA study smartphone platform (MetricWire). EMA: ecological momentary assessment.



The MetricWire app will deliver EMA surveys at four semirandom timepoints per day during participant waking hours, which will be determined at baseline. Based on the participant-defined waking hours, the first prompt will begin 30 minutes after waking time. Each of the four daily prompts will have three push notification reminders at 20, 40, and 60 minutes after the initial prompt. If the EMA survey is not completed after 60 minutes, the survey will be marked as incomplete. To fully capture instances of racism-related stressors occurring outside of random EMA survey prompts, participants will also have the option to record event-driven entries detailing their daily experiences (Figure 2, right panel). EMA surveys were designed to take no more than 3 minutes to complete to reduce respondent burden. Once per day, we will administer a brief daily diary survey via the MetricWire app to assess everyday experiences that were not determined to occur at momentary instances, including sleep-related impairment and quality, and daily experiences with racism-related stress [9]. At the conclusion of the 7-day data collection period, the study team will conduct a qualitative semistructured exit interview with each participant, and probe the participant on issues related to question difficulty and clarity, revision of question prompts, and overall satisfaction with the study protocol and EMA surveys. We anticipate the semistructured interview to last 30-60 minutes in total. Interviews will be transcribed verbatim and used to refine the EMA study protocol.

Participant Incentives

Participants will receive $100 in total, incrementally phased throughout the duration of the study to encourage higher EMA survey completion rates. Participants will receive $20 after completing the baseline survey, $20 at the completion of day three, and $20 at the conclusion of the 7-day study duration and baseline interview. Participants will receive an additional $40 if they complete at least 80% of the EMA surveys during the study period.

Safety Protocols

Previous research has demonstrated that repeated measures of suicide do not illicit suicidal thoughts or behaviors [38]. However, considering the high risk for suicide among our target sample, and to reduce the potential harm associated with repeated questions about suicide, our team will implement several safety protocols to support the mental well-being of participants enrolled in our study. Upon enrollment, participants will receive a document outlining local and national mental health resources, including suicide crisis hotlines. Additionally, all research personnel interacting with participants will be trained in psychological first aid to assist in identifying any mental health needs that arise throughout the study. EMA responses by participants will be monitored daily by the study coordinator and discussed during weekly research team meetings. Risk will be categorized in our EMA protocol using a three-tier risk designation. Moderate risk, which is defined as any suicidal ideations (“Have you had thoughts of killing yourself?”) since the last assessment, but without any plan or intent, will result in a notification to the participant guiding them to the appropriate services and urging them to seek support with their mental health outpatient provider’s phone number. Elevated risk, defined as suicidal ideation with intent or a plan within the last 24 hours (“Have you planned out how you would do it?” and/or “When you thought about killing yourself, did you think that this was something you might actually do?”), will result in the same notification given to participants with moderate risk followed by a notification to their mental health outpatient provider. In this risk category, we will also offer to contact a local crisis response hotline on their behalf. Acute risk, defined as suicidal ideation with an action since the last assessment (“Did you do anything to try to kill yourself?”), will

result in an immediate call to the local crisis response hotline made by a study team member on the participant's behalf. Safety risk alerts are programmed in MetricWire to notify the study coordinator, who will then immediately inform outpatient providers of patient responses for follow-up.

Selection of EMA Measures

To discuss the most appropriate EMA survey measures, authors (LBA, GI, EA, AD, and SJ) met weekly from November 2020 to March 2021. Based on previous EMA feasibility studies, our goal was for the duration and length of our EMA survey to last 2-3 minutes, with 20 or fewer items [17,39]. Our weekly meetings focused on measure selection as well as the suitability of each measure for the baseline survey, the EMA questionnaire, or other aspects of data collection (eg, exit survey or daily diaries).

We first identified full and brief measures related to ITS derived from our adapted conceptual framework (Figure 1), including thwarted belongingness, perceived burdensomeness, and capability for suicide [35,39,40]. We then conducted a directed literature review of brief validated measures by searching MEDLINE (PubMed) and Google Scholar to identify additional brief measures to include in our surveys. Search strategies for each database were developed in coordination with authors (LBA and SA). This search strategy included terminology related to methods (eg, digital phenotyping, smartphone, EMA), target population (eg, Black, African American), and affective states (eg, anger, fear, and happiness) relevant to our study objectives. Priority was given to studies that focused on or included our target population in the study sample and items that were previously used in EMA studies. Additional studies were also included by examining the reference lists of included studies.

To reduce validated measures into brief EMA items for our survey, we reviewed selected measures to determine their validity and reliability in our target population. We also reviewed factor analysis studies of each measure to determine items in the overall scale that were more closely related to the measured construct, incorporating items with the highest factor loading into our EMA protocol. For instance, to briefly assess hopelessness, we selected items from the Beck Hopelessness Scale with the highest factor loadings in a previous construct validity study, yielding our retention of the items "I feel that things won't work out" (item 14; 0.872 factor loading) and "I feel there is no use in really trying" (item 16; 0.912 factor loading) [33]. Finally, once items were selected, the wording of the questions was changed to reflect the real-time, momentary timing of the measures (eg, since the last prompt). Our final list of items is presented in Table 2.

Table 2. Ecological momentary questionnaire items and response options.

Measure	Items (Since the last prompt...)	Response options
Suicidal thoughts and behaviors	• Have you had thoughts of killing yourself? • Have you planned out (worked out the details of) how you would do it? • When you thought about killing yourself, did you think that this was something you might actually do? • Did you do anything to try to kill yourself?	Yes or No
Suicidal intensity	• How intense is this feeling for you right now?	Likert scale 1-10
Depression [34]	• I have little interest or pleasure in doing things • I am feeling down, depressed, or hopeless	Likert scale: 0=Not at all, 1=Some of the time, 2=Most of the time, 3=All of the time
Thwarted belongingness [35]	• I feel close to others • I feel like I belong	Yes or No
Perceived burdensomeness [25]	• I feel that people would be happier without me • I feel that right now people would be better off if I was gone	Yes or No
Hopelessness [33]	• I feel that things won't work out • I feel there is no use in really trying	True or false
Capability for suicide [40]	• I could kill myself if I wanted to. • I am very much afraid to die.	Likert scale 1-10

Acceptability and Feasibility

Feasibility will be assessed by the following: (1) the ratio between the number of people who enroll in the study and the total number of people approached for recruitment and/or who complete a screening survey, (2) participant reports of ease of completing the EMA survey (Likert scale: 1-5), (3) percentage low compliance (defined as 50% or fewer EMA surveys completed during the 7-day period), (4) percentage of safety-related incidents reported to clinical staff (eg, acute suicide risk notifications), and (5) average length of time to complete surveys. Acceptability will be assessed using qualitative responses from semistructured exit interviews at the end of data collection. Participants will also have the option to

write free-text responses reflecting upon the acceptability of the study.

Data Analysis

To address known issues with missingness associated with EMA survey compliance [17], we will include only respondents who completed 50% or more of their EMA surveys. We anticipate that our estimated sample size of 50 participants will yield 1120 completed EMA survey responses (accounting for 80% compliance), 350 daily diary responses, and 50 baseline questionnaire surveys for subsequent cross-sectional and longitudinal analyses. Descriptive statistics will be used to characterize the study population in terms of baseline characteristics and feasibility measures using means, *t* tests, chi-square tests (categorical outcomes), and bivariate correlations (continuous outcomes). Descriptive statistics will be summarized by EMA survey compliance (eg, <50%, ≥50%, and ≥80%). We will compute Cronbach α and item-to-total correlations of baseline survey measures. Differences in survey compliance based on baseline characteristics will also be examined using linear regression.

Our primary analysis will investigate the hypothesized mediation model in Figure 1, which will assess the influence of racism-related stressors on suicide outcomes, through the mediating influence of ITS constructs (eg, thwarted belongingness, perceived burdensomeness, and hopelessness). We will conduct multilevel mediation path models using randomly prompted EMA data in Mplus (version 8.4), accounting for the hierarchical data structure of the repeated EMA signals (level 1: within subject) nested within participants (level 2: between subjects) [41]. We will employ maximum likelihood estimation approaches to account for missing data. Tests for moderation will be conducted by using cross-level interactions in the mediation model. Once significant (P<.05) predictive, mediating, and moderating factors are identified, we will extract the following information for each significant variable to sufficiently power future multilevel intervention studies: means, variances, parameter estimates, and patterns of missingness.

Qualitative responses from respondent-driven recordings of racism-related events will be analyzed using an iterative thematic approach [42,43]. Recorded events will be professionally transcribed verbatim. Deidentified transcripts will be uploaded onto Dedoose software for subsequent analysis [44]. Final qualitative themes will enhance our understanding of daily experiences of racism among a psychiatric sample of Black men.

Results

Research team meetings to select and modify measures for our study resulted in a 15-item EMA survey administered 4 times per day and a 22-item daily diary survey administered at the end of each day. As of July 2021, recruitment for the qualitative phase of our mixed methods study is currently underway. Inclusion of participants for the EMA phase of our study will begin as early as August 2021 and will conclude by December 2022. Complete data collection and analyses are expected to conclude by February 2023. Preliminary results are expected to be disseminated in peer-reviewed journals and presented at national conferences starting in Spring 2022. All phases of the research study have been approved by the Institutional Review Board at Johns Hopkins Bloomberg School of Public Health (#00013672).

Discussion

Principal Findings

The anticipated results of the study will inform how racism-related stressors influence both proximal risk factors and suicidal thoughts and behaviors in a psychiatric sample of Black young adult men. The significance of the research provides timely explanatory evidence toward the growing trend of suicide completion among Black men, who comprise the largest percentage of deaths by suicide (81%) within the Black community [5]. The goal of this protocol is twofold: (1) to demonstrate the suitability of EMA methods in assessing real-time momentary changes of suicidality within Black men and (2) to clarify the temporal role of real-time racism-related stressors in the experiences leading to suicidal outcomes. The proposed research is the first to our knowledge to address critical research gaps in suicide research, including the consideration of racism-related stress in the theoretical and empirical application of the ITS. Additionally, our research team plans to leverage the full promise of intensive longitudinal data collection procedures using EMA and daily diary surveys among a within-group sample of Black men, an underrepresented and understudied population in suicide prevention research.

Limitations

Participant burden, noncompliance, and reactivity to the protocol measures have been cited as potential limitations to EMA and smartphone-based mobile health studies [18,45]. We are encouraged by extant research demonstrating a median response rate of 75% or higher over longer periods among psychiatric patients and young adults [21,46-49]. To encourage steady compliance, participant incentives will be distributed incrementally, which has been done successfully in previous studies [45]. In the event of steady poor compliance and reduced yield of expected observations, we will leverage the following: (1) completed EMA surveys collected at earlier time points (eg, day 1 and day 2 of the 7-day study), (2) the daily diary, and (3) baseline cross-sectional survey responses. This study is also limited in its generalizability to Black men receiving psychiatric care in an academic research hospital in Baltimore, MD. Future studies should consider additional venues and settings to recruit Black men who are not engaged in psychiatric care, including but not limited to social media, advocacy groups, and peer-led and/or community-based organizations.

Conclusions

Despite these limitations, our proposed study has the potential to more robustly identify and assess the impact of daily racialized stressors among Black men with mental health needs. Study results will provide insights regarding the temporal influence of frequent racism-related stress, which can be clarified further and potentially mitigated in future suicide

prevention research across multiple settings. Findings from this study will also generate key hypotheses for future fully powered EMA and intervention research that includes information on missingness patterns, compliance, and parameter estimates of key study variables. In addition to assessing the suitability of EMA approaches to capture daily racialized experiences and proximal suicide outcomes, our findings can be adapted to other ecologically valid contexts that may exacerbate Black young adult men's mental health outcomes in real time, such as police killings of unarmed Black men and other direct and vicarious experiences of racial trauma [50,51]. Overall, our study will provide important insights to help bridge the gap in research regarding Black men's suicidality and will serve as a model for future real-time smartphone-based assessments focused on this vulnerable population.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review response from the American Foundation of Suicide Prevention.
[PDF File (Adobe PDF File), 316 KB - resprot_v10i10e31241_app1.pdf]

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Abbreviations

EMA: ecological momentary assessment
ITS: Interpersonal Theory of Suicide

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Protocol

Understanding Adolescent and Young Adult 6-Mercaptopurine Adherence and mHealth Engagement During Cancer Treatment: Protocol for Ecological Momentary Assessment

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Abstract

Background: Adolescents and young adults (AYAs) with cancer demonstrate suboptimal oral chemotherapy adherence, increasing their risk of cancer relapse. It is unclear how everyday time-varying contextual factors (eg, mood) affect their adherence, stalling the development of personalized mobile health (mHealth) interventions. Poor engagement is also a challenge across mHealth trials; an effective adherence intervention must be engaging to promote uptake.

Objective: This protocol aims to determine the temporal associations between daily contextual factors and 6-mercaptopurine (6-MP) adherence and explore the proximal impact of various engagement strategies on ecological momentary assessment survey completion.

Methods: At the Children's Hospital of Philadelphia, AYAs with acute lymphoblastic leukemia or lymphoma who are prescribed prolonged maintenance chemotherapy that includes daily oral 6-MP are eligible, along with their matched caregivers. Participants will use an ecological momentary assessment app called ADAPTS (Adherence Assessments and Personalized Timely Support)—a version of an open-source app that was modified for AYAs with cancer through a user-centered process—and complete surveys in bursts over 6 months. Theory-informed engagement strategies will be microrandomized to estimate the causal effects on proximal survey completion.

Results: With funding from the National Cancer Institute and institutional review board approval, of the proposed 30 AYA-caregiver dyads, 60% (18/30) have been enrolled; of the 18 enrolled, 15 (83%) have completed the study so far.

Conclusions: This protocol represents an important first step toward prescreening tailoring variables and engagement components for a just-in-time adaptive intervention designed to promote both 6-MP adherence and mHealth engagement.

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KEYWORDS

mHealth; ecological momentary assessment; adolescents; young adults; oncology; cancer; self-management; mobile phone

Introduction

Background

For patients with acute lymphoblastic leukemia or lymphoma, durable cancer remission requires a prolonged maintenance phase characterized by 18-30 months of a regimen that includes daily oral intake of the chemotherapy agent 6-mercaptopurine (6-MP) [1,2]. In a trial conducted by the Children's Oncology Group, nearly 50% of children and adolescents demonstrated electronically monitored 6-MP adherence rates below a 95% critical level for relapse prevention, resulting in a 2.5 times greater risk for relapse in nonadherent patients [1]. In this study and others, adolescents and young adults (AYAs) with cancer demonstrated lower oral chemotherapy adherence than their younger counterparts [2-6]. AYA treatment adherence is often at odds with normative developmental goals, such as establishing autonomy and navigating social pressures, as well as neurodevelopmental changes that occur during these years (eg, developing executive functions) [7-9]. Although cross-sectional studies have begun to identify contextual risk factors for oral chemotherapy nonadherence, including physical symptoms [10,11], negative mood [10,12], low motivation [13,14], difficult family interactions [15-17], and environmental factors (eg, being outside of the home) [15,17,18], these multifactorial and dynamic contexts can vary from day to day within individuals [19]. It remains unclear how these idiosyncratic factors affect daily 6-MP adherence, complicating the development of personalized mobile health (mHealth) interventions to deliver effective, contextualized, and timely adherence support [20-23]. For addressing this gap, this paper describes the protocol for an app-based ecological momentary assessment (EMA) study of AYAs with cancer.

EMA involves frequent surveys about behaviors and experiences in real time, often via SMS text messaging or mobile apps [24-26], making it a particularly appealing methodology for native smartphone users such as AYAs. EMA offers several distinct advantages for advancing adherence science by reducing recall bias, increasing real-world generalizability, and providing multilevel data on how adherence behaviors play out over time, place, and context [27]. In a pilot study, we demonstrated that implementing daily EMA for 6-MP adherence, across 28 days, was feasible and acceptable for AYAs with leukemia [28]. AYAs were more likely to miss a dose of 6-MP on weekends and on days when their adherence motivation and negative affect were worse relative to their typical functioning. Although these findings were novel and offered potential decision rules to test in future trials (eg, *deliver a medication reminder on weekends when AYA may be more prone to forget*), they require replication with a larger sample, over a longer period of time, and including AYA's caregivers who are often intricately involved in cancer medication management (in one study, 73% of caregivers were responsible for managing these medications) [17].

A challenge with EMA and mHealth tools, in general, is rapidly declining user engagement [29-32]. All the methodological advantages of EMA are weakened if participants miss substantial surveys or stop responding altogether [29]. Moreover, AYAs with the greatest treatment adherence challenges—who would stand to benefit the most from an adherence-promotion intervention—may be the least likely to engage with EMA [28,33]. Although our pilot study demonstrated relatively high and stable EMA survey completion rates (mean 88.9%, SD 16.7%), there was substantial variability (range 39.3%-100%), and users were compensated US $2 for completing all 14 survey questions per day (up to US $56 total across 28 days) [28]. Financial incentives are an effective method to promote mHealth engagement in the short term; however, evidence supporting their long-term efficacy is mixed, and they may not be scalable in real-world clinical settings [34].

Just-in-time adaptive interventions (JITAIs) use tailoring variables (eg, information about a participant used to make decisions, such as perceptions of mood, motivation, and family interactions) and decision rules (eg, specifying which intervention to offer and to whom, based on the tailoring variable) to deliver interventions adapted to the participant's internal and external states [35]. At this time, many of the hypothesized contextual tailoring variables related to 6-MP adherence (eg, motivation and family functioning) can only be collected via EMA (rather via sensors). Thus, identifying lower cost and effective EMA engagement strategies is an essential prerequisite for the design of clinical trials that optimize adherence-promotion interventions and even eventual real-world implementations of strategies identified to be effective.

Various fields, including psychology, human-computer interaction, and marketing, highlight alternative strategies for engaging individuals. Engagement strategies may include social influence tactics (eg, targeting reciprocity by providing a *no strings attached* reward to increase the likelihood of later completing a survey) and operant conditioning behavioral principles (eg, receiving a desirable reward that reinforces survey completion) [36]. Rewards may facilitate extrinsic motivation (eg, completing a survey as it results in something immediately gratifying, like a funny meme) or intrinsic motivation (eg, completing a survey as the data will help someone else) [37]. To date, limited research has focused on optimizing such engagement strategies in mHealth tools, where the ultimate goal is to dynamically adapt engagement components to match the unique characteristics and changing responses of users [36].

Objectives

In this study, we adopted and refined an open-source EMA app called SARA [38] for an AYA cancer population (renamed ADAPTS [Adherence Assessments and Personalized Timely Support]). Through using this app, our primary study aim is to determine the temporal associations between daily contextual factors and 6-MP adherence. We draw on the pediatric self-management model [39], a social-ecological theoretical framework of disease self-management and treatment adherence, focusing primarily on the individual-and family-level contexts

that could affect day-to-day medication adherence. Specifically, we hypothesize that daily fluctuations in intrapersonal (eg, physical symptoms, negative mood, and low motivation) and interpersonal or environmental (eg, a dyadic AYA-caregiver disagreement and being outside of the home without caregivers) factors will increase the odds of missing 6-MP that day. In a secondary exploratory aim, we will explore the proximal impacts of theory-informed engagement strategies (reciprocity and nonmonetary reinforcements) on daily EMA survey completion. Our approach is consistent with the first step of the Behavior Change Theories, User-Centered Design, and Social Marketing framework, a comprehensive model for creating mHealth tools, which recommends conducting a situational analysis of the contextual factors associated with a health problem [40], as well as the preparation phase of the multiphase optimization strategy [41] comprised of gathering initial information to decide which set of (engagement) components to include before an optimization trial. These formative data will ultimately inform the creation of the first JITAI for improving AYA oral chemotherapy adherence while running a concurrent JITAI for promoting EMA engagement. Improving the precision of adherence-promotion interventions in this manner may significantly benefit AYAs who require frequent self-administration of medications, as static interventions have yielded small and heterogeneous effects [42,43].

Methods

Study Design

This study uses an intensive longitudinal burst design to periodically deliver EMA surveys over 6 months of maintenance chemotherapy that includes daily prescribed oral 6-MP to AYAs with acute lymphoblastic leukemia or lymphoma and their caregivers. Within the observational EMA study is an embedded microrandomized trial—an experimental design for optimizing mHealth interventions [29]—that randomizes engagement components within person and across EMAs as an early check on their efficacy before incorporating and piloting in a later JITAI.

At baseline, the enrolled AYAs and their caregivers will complete a demographic survey; brief screening measure of executive functioning; and assessment of COVID-19 exposure, impact, and distress [44] via REDCap (Research Electronic Data Capture; Vanderbilt University). Using the ADAPTS app, each participant will then receive EMA in *bursts* over the course of 6 months of maintenance therapy, capturing a time frame known to be associated with AYA 6-MP nonadherence and cancer relapse. In month 1 (28 days; ie, burst 1), EMA surveys will be sent once per day via the app to fully capture contextual processes during the month between follow-up medical appointments. To balance participant burden while also ensuring data are representative, in months 2-6, EMA surveys will be delivered once per day at the same time (6 PM), for one full week (2 weeks after the last maintenance appointment to approximate the midpoint between clinic visits when the AYA may have decreased adherence; for 35 days total), resulting in *bursts* of EMA data collection [45]. Burst designs such as this have been used to study other AYA health behaviors over a longer period [46]. Each AYA will receive a MEMS TrackCap (AARDEX Group), a validated electronic adherence monitor that was also used in the Children's Oncology Group study, to measure daily 6-MP adherence across the entire study period.

EMA surveys are brief (<1 minute to complete) and assess intrapersonal contexts (eg, individual-level variables, such as nausea, fatigue, and positive or negative affect) and interpersonal contexts (eg, family and social environment variables, such as recent family interaction and location). Enrolled AYAs will complete 11 daily survey questions, and their caregivers will complete four survey questions (see Table 1 for a complete list of survey items).

Table 1. Ecological momentary assessment (EMA) survey questions.

Variable	Informants	Items	Description
Intrapersonal contexts			
Physical symptoms	AYA[a]	• How much pain are you currently experiencing? • How much fatigue are you currently experiencing? • How much nausea are you currently experiencing?	Three items assessing the intensity of current pain, fatigue, and nausea on a scale of 0 (not at all) to 4 (extremely); adapted from two adult oncology EMA studies [47,48]
Positive and negative effect	AYA and caregiver	• How positive were you feeling (happy or joyful) just before you received this text message? • How negative were you feeling (stressed, mad or angry, nervous or anxious, or sad) were you feeling just before you received this text message?	Two items assessing the degree of positive affect and negative affect on a scale of 0 (not at all) to 4 (extremely); adapted from a physical activity EMA study [49,50]
Adherence motivation	AYA	• How motivated are you to take 6-MP[b] today?	One item assessing motivation to take 6-MP on a scale of 0 (not motivated) to 4 (extremely motivated); adapted from EMA study of medication adherence in adults with HIV [51]
Interpersonal and environmental contexts			
Family or social stressors	AYA and caregiver	In the past 24 hours, have you • Had a misunderstanding or disagreement with your parent or child? • How easy was it to talk to your parent or child about your thoughts and feelings? • (AYA only) How lonely are you currently feeling?	Three adapted items from the Hassles Scale for Children [52] and an EMA study of adolescents with asthma [53], assessing whether or not the AYA experienced a disagreement or misunderstanding with parents and ease with communication and loneliness on a scale of 0 (not at all) to 4 (extremely)
Location or social company	AYA	• Where were you right before you received this survey? • Who were you with just before you received this survey?	Two items assessing where the AYA was (home, school, car, outdoors, restaurant, store, someone else's house, gym, or someplace else) and who they were with (alone, mom or dad, sister or sisters, brother or brothers, other family, friend or friends, classmate or classmates, or someone else); adapted from EMA studies of diabetes adherence [54], physical activity [49,50], and asthma symptoms [53]

[a]AYA: adolescent and young adult.

[b]6-MP: 6-mercaptopurine.

Setting and Recruitment

We are currently recruiting eligible participants at the Children's Hospital of Philadelphia (CHOP) Cancer Center during routine maintenance chemotherapy outpatient visits. Eligible participants will be provided with study advertising materials, including a study flier and a live demonstration of the ADAPTS app. Considering the COVID-19 pandemic, the protocol also includes procedures that allow for remote recruitment (eg, enrollment over the phone with verbal consent).

Inclusion and Exclusion Criteria

This study will include 30 AYAs with leukemia or lymphoma in the maintenance phase of treatment and 30 of their matched caregivers. The inclusion criteria for AYAs are as follows: (1) aged 14-25 years; (2) diagnosed with acute lymphoblastic leukemia or lymphoma; (3) in the maintenance phase of treatment and completed at least 1 month of maintenance chemotherapy with at least 6 months remaining; (4) prescribed daily oral 6-MP; (5) English language proficiency; and (6) AYAs aged <18 years must have a caregiver (parent or legal guardian) to provide informed consent. The exclusion criterion for AYAs is cognitive impairments that would limit their ability to complete measures, as determined by their medical team. The inclusion criteria for caregivers are as follows: (1) nominated by an AYA as a caregiver involved in oncology care and (2) lives in the same household as the AYA (given this study's focus on family-level processes that could affect 6-MP adherence).

App Platform and Refinement Process

EMA surveys will be delivered via an open-source app called ADAPTS. ADAPTS is a modified version of an existing app called SARA [38]. In the original trial, SARA delivered daily surveys to AYA at risk for substance abuse for 30 days and provided a variety of theory-informed and developmentally relevant engagement strategies. Specifically, in addition to small amounts of money (US $1 for every 3 consecutive days of daily self-reporting), SARA provided nonmonetary incentives for completing surveys that were grounded in operant conditioning

principles (eg, reinforcing survey completion with funny memes) and had a user-centered and gamified data collection environment (ie, an aquarium that became increasingly complex by unlocking fish as users completed surveys). To promote reciprocity, SARA also provided an unsolicited reward (an inspirational celebrity quote) before delivering the EMA survey. This app demonstrated slightly lower levels of EMA engagement compared with other substance abuse studies but with much smaller financial incentives (mean 62.3% surveys completed, mean 18.1 out of 30 days, SD 9.2; mean US $6.24, SD 3.83; range, US $1.00-$13.00 money earned). Engagement strategies were microrandomized to determine whether a particular strategy (eg, rewarding a meme after a survey was completed) proximally affected survey completion in the next time window (eg, the next day). The results provided preliminary support for the use of a reciprocity strategy in future trials.

Informed by user-centered design and agile science principles [40,55], our research team iteratively refined SARA for AYAs with cancer over four stages. First, we convened a multidisciplinary team of behavioral scientists and technologists to identify possible app modifications that could improve the app's functionality and accommodate differences in this study's methods or population. The following app modifications were made: (1) expanded the app to accommodate this study's longer EMA period of 63 days (eg, including progressing the environment to grow from an aquarium into other levels); (2) developed a parallel caregiver version; (3) identified and vetted contemporary engagement content that would be particularly relevant to AYAs with cancer (ie, new memes and celebrity quotes); (4) delivered a survey reminder if EMA was not completed; and (5) incorporated one new engagement strategy—altruistic thank you messages for completing surveys (an other-benefitting incentive [37] that targets intrinsic motivations for helping other AYAs with cancer).

Second, stakeholders, including a convenience AYA sample (4 AYAs with a history of cancer involved in a hospital-based steering committee and 1 AYA without cancer) and 18 AYA oncology providers and research staff, rated 66 memes and 100 celebrity quotes identified from social media or web searches on a 5-point scale (from 1="Do not like at all, do not recommend including" to 5="Really like, use this"), which were narrowed to the most highly rated (>3.5/6) content (resulting in a final bank of 31 memes and 72 quotes). Third, we conducted a 1-month internal pilot test with oncology providers and research staff (n=8) to assess app glitches and elicit further feedback on the design and features. Research staff observed technical glitches (eg, surveys not registering when the device was offline and reminders sent at the wrong times) and provided additional suggestions for improving the app's functionality (eg, storing previously received rewards in a feed like other popular social media apps). These glitches and suggestions were addressed before a 1-month pilot with AYAs with cancer (n=10). Finally, in the pilot with end users, AYAs generally reported high satisfaction with the app, and a few remaining technical problems were resolved (eg, malfunction with the survey submit button).

Study App (ADAPTS)

The finalized version of ADAPTS delivers EMA surveys to the AYAs and their caregivers, as well as several engagement strategies (Figure 1). The app is available for both iPhone and Android users. Surveys are available between 6 PM and midnight. If the surveys are not completed by 8 PM, participants will receive a reminder. Automated engagement strategies will include the following: (1) pre-EMA nonmonetary engagement strategies (inspirational celebrity quotes and survey reminders; Multimedia Appendix 1 for a complete list of quotes); (2) post-EMA nonmonetary rewards (funny memes, altruistic messages, and a growing virtual environment from an aquarium to an ocean, tundra, and then a rainforest; Figure 2 and Multimedia Appendices 2 and 3 for complete lists of memes and altruistic messages); and (3) post-EMA small monetary rewards (US $2 for completing surveys on every first day of a new EMA cycle, then US $1 for every 3-day streak with 100% completion of surveys).

Figure 1. Schedule of ecological momentary assessment and engagement features for adolescent and young adult participants. EMA: ecological momentary assessment.

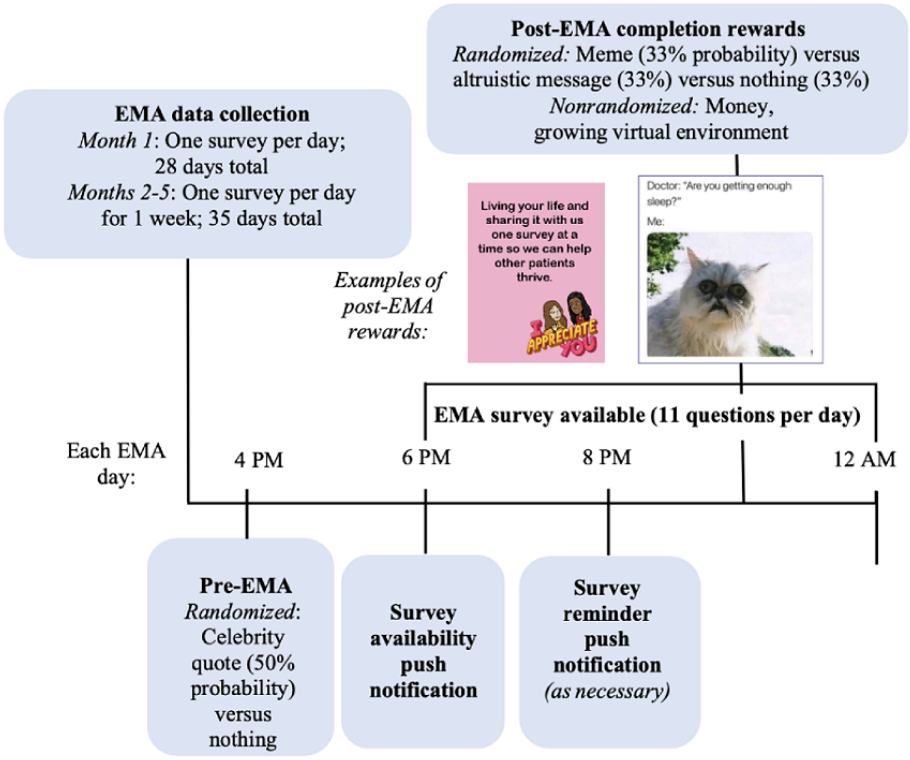
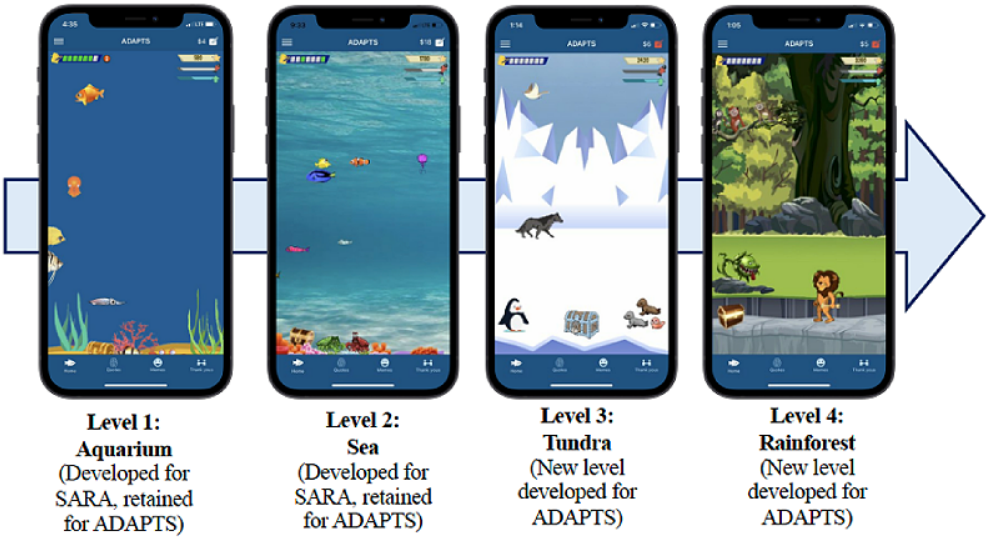


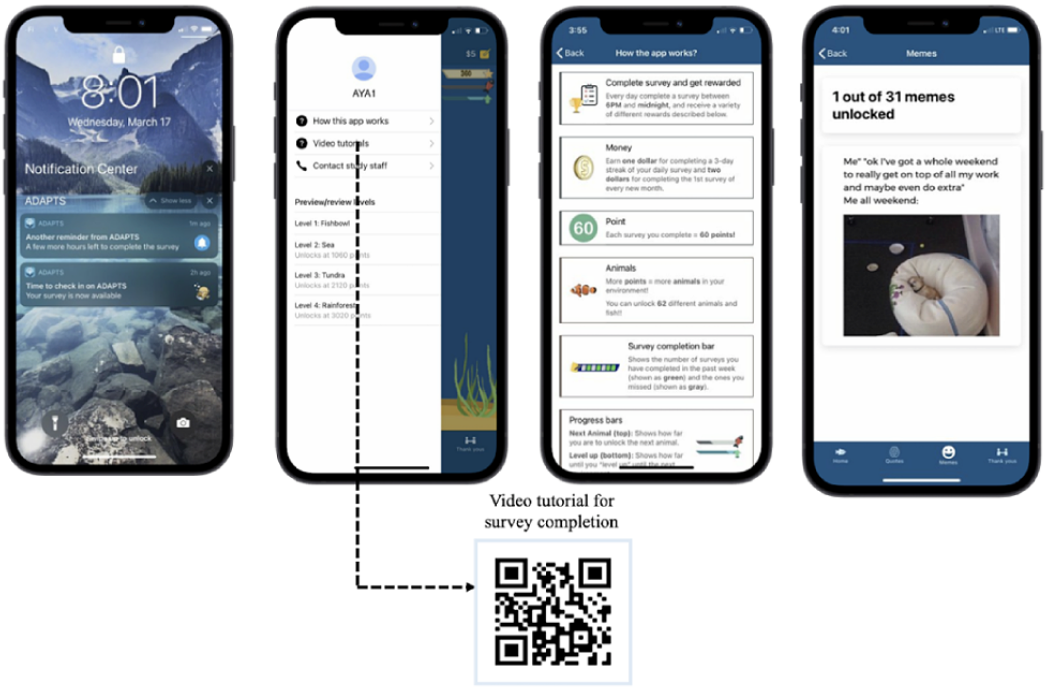
Figure 2. App environment expansion. ADAPTS: Adherence Assessments and Personalized Timely Support.



Participants can provide feedback on certain engagement content (ie, celebrity quotes, memes, and altruistic messages) by liking or disliking each with a *thumbs up* or *thumbs down* button. Previously received engagement content will be stored in a feed. Each time participants unlock an animal or other content (eg, snow in the tundra) in the virtual environment (72 total, for approximately 1 new addition per EMA day), they will receive a fun fact (eg, "No penguins live in the north pole"; see Multimedia Appendix 4 for a complete list of animals and facts). Some content in the virtual environment is interactive, such as animals jumping when they are touched and turning on and off snow or rain. Other included app content includes a *how this*

app works visual; video tutorials; a contact study staff page to directly call, text, or email the study coordinator; and survey completion and app progress bars to provide feedback and show when the participant will *level up* (Figure 3).

Figure 3. Other app features: push notifications, education, and reward storage.



Microrandomization

Before the EMA survey being sent, participants will be randomized every day at 4 PM, with a probability of 0.5, to receive a push notification with an inspirational celebrity quote or to receive nothing (Figure 1). Consistent with the original SARA app, this incentive will be sent before the EMA survey is available to facilitate reciprocity; that is, to increase the likelihood that participants will *return the favor* by completing the survey when it is later available. After the EMA survey is completed, participants will be randomized with a 0.33 probability of receiving a funny meme (targeting extrinsic motivation), an altruistic message (targeting intrinsic motivation), or nothing. The other engagement strategies (ie, money and growing virtual environments) will not be randomized. The caregiver version of the app includes nonmonetary rewards (same growing virtual environment) and small monetary rewards (same compensation schedule) but does not include AYA-focused memes or quotes.

Human Support and Monitoring

In addition to automated engagement strategies integrated within the app, there are a few prompts that are manually sent by a member of our study team. First, after completing the first week of EMA, a standardized SMS text message will be sent to each AYA or caregiver participant to inquire about app glitches and provide a reminder to use the electronic pill bottle. Second, when a participant does not answer surveys for 3 consecutive days, they will receive an additional standardized SMS text message offering in-the-moment support for any app glitches for a maximum of one time during each EMA burst. Third, each month, a research assistant will meet briefly with families during monthly clinic visits to remind them of the study, ensure that the family is refilling MEMS bottles with 6-MP, confirm that AYAs and caregivers still have access to ADAPTS, provide financial compensation for their participation in the prior month, and download adherence data from the prior month as well as share with the AYA's primary oncology provider. This level of human support is similar to our other prior mHealth trials [31], including the SARA trial.

To monitor for technical glitches, study staff will pull survey and engagement data each day to review whether (1) participants completed the survey from the prior day, (2) the money earned corresponds with the intended payment schedule, (3) the push notifications were sent and at the right times, and (4) participants are using the most up-to-date version of the app. Study staff will also review the list of active study participants and manually turn surveys *on* and *off* depending on their EMA burst cycle. Any technical issues will be documented in a log and shared with a technology support team within 24 hours.

Data Management and Security

Raw EMA and app engagement data do not contain Protected Health Information and will be temporarily stored in an encrypted form, with a unique study ID, in the ADAPTS app on the smartphone. When connected to the internet, encrypted data will be transferred continuously to CHOP's secure Enterprise Amazon Web Services S3 data repository, which supports data redundancy; local EMA data on the smartphone will be deleted after successful transfer. Data will be backed up each night to a separate S3 data repository. If a participant does not connect to the internet, then the data will be temporarily

stored on their smartphone. The research team also developed a password-protected study monitoring website on the CHOP network. The study monitoring website is a tool for quickly reviewing each participant's EMA completion rates (depicts survey completion at the daily and aggregate levels) and money earned across EMA days. It is also where the RA can turn surveys on or off.

Primary Outcome

The primary outcome is daily 6-MP adherence, measured using a validated electronic medication bottle called MEMS TrackCap. MEMS TrackCaps have two parts: (1) a standard plastic vial that stores pills and (2) a lid that contains a sensor that registers times when the vial lid is opened and closed. This method of electronic adherence monitoring has been validated in pediatric cancer, has shown consistent accuracy in independent testing, and was the same measure used in the Children's Oncology Group study that established a 95% critical adherence level needed for relapse prevention [1,56,57]. The accompanying medAmigo software (AARDEX Group) displays the timestamped adherence data for each day. Participants will be instructed to place 6-MP in the MEMS within 24 hours of enrollment, use the MEMS each day for the full duration of the 6-month study (rather than a pillbox or pharmacy bottle), and only open the bottle if they are taking 6-MP or refilling the bottle at that time. For each day, 6-MP adherence will be classified as 1 (took dose) or 0 (missed dose).

Secondary (Exploratory) Outcome

We will explore whether the microrandomized engagement content proximally affects EMA survey completion, classified as 1 (completed survey) or 0 (did not complete survey). For the celebrity quotes delivered at 4 PM, the proximal outcome is whether the survey is completed in the evening on the same day. For the post-EMA rewards (altruistic thank you messages and memes), the proximal outcome is whether the survey is completed on the following day.

Primary Data Analyses

This data set will consist of 30 AYA-caregiver dyads×63 days=a maximum of 1890 daily observations. EMA predictors include data from AYAs, caregivers, or dyadic data from both reports (eg, agreement between AYAs and caregivers that they had a disagreement that day). Tables and graphs will be created to demonstrate how 6-MP adherence varies by individual (physical symptoms, mood, and motivation), family (family disagreements and problems with communication), and social-environmental factors (time of day, day of the week, month of the year, where AYAs were, and who they were with). Mixed effects models will be used through SAS PROC GLIMMIX (SAS Institute) to examine whether EMA of contextual factors predicted the binary daily 6-MP adherence outcome. Separate mixed effects models will be constructed for different predictors and include the predictor as the fixed effect and a random intercept for each participant to account for between-person variability. Mixed effects models may also include demographic and treatment covariates (eg, race, ethnicity, and time since cancer diagnosis) as fixed effects if they demonstrated a significant association with the outcome. We will decompose the between-subject and within-subject effects of EMA of contextual factors by creating two predictors from the original score: (1) the individual mean across all time points (between-subject predictor) and (2) the deviation of the daily score from the individual mean (within-subject predictor). Given the embedded engagement strategies, we expect minimal missing data, and mixed effects modeling will be able to use all available outcome data and provide valid inferences if missingness is at random. However, we will examine the amount and pattern of missing data, and if missing is suspected to be not at random, sensitivity analyses will be performed to assess the robustness of the primary analysis results. Significant findings will inform tailoring variables for future JITAIs (eg, tailor messages based on affect, motivation, and day of week).

Exploratory Analyses

We will analyze microrandomized trial data with a regression-based approach that was specifically developed to ensure unbiased estimates of the causal effects of time-varying treatments [58]. These analyses pool time-varying, longitudinal data across participants and use a log-link function to accommodate the binary outcome (survey completed vs not completed). The causal effect is expressed on the risk-ratio scale that measures the probability of proximally completing an EMA survey when an engagement strategy is deployed, divided by the probability of proximally completing an EMA survey when the engagement strategy was not deployed. To test the effect of reciprocity, proximal survey completion refers to the current day. For nonmonetary reinforcements that are delivered after the EMA survey is completed (memes and altruistic messages), proximal survey completion refers to the next day. Two separate analyses will be conducted: (1) examining the main effect of reciprocity (vs nothing) with the celebrity quote and (2) examining the main effects of the meme reinforcer versus altruistic message versus nothing. The risk ratio will be >1 if offering (vs not offering) the engagement strategy has a causal effect on the probability of proximal survey completion. These exploratory analyses will prescreen engagement components to retain in the JITAIs.

Sample Size and Power

Power calculations were performed using the PASS 2021 [59]. With 63 days of repeated measures and assuming a moderate within-subject correlation of 0.5, the most effective sample size for predicting our binary adherence outcome (took dose vs not) is 59 AYAs [60]. However, our study sample size is constrained by the available AYAs who meet the inclusion criteria at our single institution. With our proposed sample size of 30 AYA-caregiver dyads, assuming a two-sided type 1 error of 0.05 and an approximate nonadherence rate of 20% (based on estimates from prior studies) [28,61], we will have 80% power to detect an odds ratio of 2.8 (a large effect) for every 1 SD increase in a continuous predictor [62].

Results

This study received funding from the National Cancer Institute on September 1, 2019 (K08CA241335), institutional review board approval at CHOP on September 24, 2019, and began recruiting in June 2020. To date, of the proposed 30

AYA-caregiver dyads, 18 (60%) have been enrolled, and 15 (50%) have completed the 6-month study. We expect data collection to be completed by June 2022.

Discussion

Overview

In response to empirical and clinical data that have demonstrated suboptimal 6-MP adherence rates among AYAs and increased cancer relapse risk [1], we designed this app-based EMA study to identify the states that change rapidly (eg, mood and fatigue) and proximally affect an AYA's adherence to taking the prescribed daily oral 6-MP. As a pervasive threat to mHealth is declining user engagement, we have incorporated theory-informed and user-centered engagement features within the app, and we will explore their proximal relationships with EMA engagement. Together, these aims represent important first steps toward translating daily contextual data into personalized and engaging adherence support. As such, our protocol is consistent with a paradigm shift toward precision health [19] and the first stages of the Behavior Change Theories, User-Centered Design, and Social Marketing and multiphase optimization strategy intervention development frameworks [40,41]. Study innovations also include (1) collecting multilevel EMA data from both AYAs and their caregivers, which is informed by a social-ecological theory of disease self-management; (2) obtaining EMA data in bursts over a longer period, with support from low-cost engagement strategies; (3) using an open-source EMA app, which is cost effective and increases the generalizability of methods; and (4) microrandomizing EMA engagement strategies to explore their proximal impact on survey completion, helping lay the groundwork for selecting engagement components for the later JITAIs.

An optimized JITAI is well suited to address the gaps in prior adherence-promotion interventions by maximizing engagement, minimizing burden, and delivering a personalized intervention only when there is a true benefit [35]. Consistent with the broader pediatric adherence-promotion literature [42,43], effect sizes from a few existing and static 6-MP adherence-promotion interventions are small and possess key limitations (eg, suboptimal participant engagement in digital health components and relying on parental supervision of medication taking, which may not be feasible or acceptable to an AYA population) [63,64]. Moreover, optimization questions regarding which intervention option to offer to AYAs and when have been neglected. The results from this EMA study will serve as an initial check of the time-varying contexts that are salient for 6-MP adherence, which will help inform the EMA questions that will be retained and used as tailoring variables in the JITAIs. Moreover, this study will help prescreen engagement components that will be further piloted in the intervention.

Future Directions

The next phase of this 6-MP adherence research is to engage with a multidisciplinary research team (including experts in behavioral science, mHealth, oncology, AYA development, and health communications), along with AYA cancer representatives, to identify an initial set of tailoring variables, decision rules, and self-management intervention options for the JITAIs. For example, a tailoring variable may be *adherence motivation*, a self-management intervention component may be *goal congruence*, and a decision rule may be *deliver if motivation decreases by X points*. We will use an intervention mapping–informed approach [65,66] to ensure that each JITAI component is grounded in self-management theory and existing empirical evidence (including results from the present EMA study). Mobile messages that map onto the tailoring variables, decision rules, and intervention components will then be created through an iterative process with the research team and AYA stakeholders, with members suggesting and revising the content to be theory grounded, developmentally appropriate, specific to intervention goals, and at a sixth grade reading level. A smaller subset of AYAs from the EMA study will be invited to participate in a focus group to provide feedback on this initial prototype.

Another future direction is understanding the contexts (eg, mood, family interactions, and weekends) in which mHealth engagement strategies are the most effective. Data from this study and others could inform reinforcement learning algorithms to increase the probability of providing an engagement strategy that is the most effective for an individual in a particular context. It will also be important to build an evidence base to understand the generalizability of engagement strategies across populations. For example, it is possible that our population—AYAs who have recently entered remission for their cancer treatment—may be more responsive to altruistic reinforcements that remind them that they are helping other cancer patients, compared with other AYA groups. To achieve effective adherence to JITAIs, we also need to develop effective engagement JITAIs to promote the uptake of adherence-promoting content.

Limitations and Anticipated Challenges

First, although our study focuses on adherence to the most common oral chemotherapy prescribed to pediatric cancer patients (6-MP), it is not designed to assess adherence to other cancer-related medications (eg, prophylactic antibiotics). AYAs taking 6-MP as maintenance chemotherapy are an exemplar relatively homogenous disease cohort with known adherence challenges with which to test new methods of adherence observation and intervention. However, expansion to other AYA oncology populations, who have understudied adherence patterns, will be essential in future studies. Second, our sample size and power are not optimal to detect small to medium effects. Although our cancer center is one of the largest pediatric centers in North America, the age and diagnosis inclusion criteria for our study are strict (to reduce heterogeneity), which narrows the available AYA population to recruit. Moreover, our observation period of 63 days does not capture the full duration of maintenance chemotherapy in this population (approximately 18 months). Nonetheless, this study nearly doubles the number of participants and daily observations that were included in our pilot EMA study [28] and offers an important opportunity to replicate significant findings. It will be important that a later JITAI optimization trial include multiple sites to recruit a larger and more demographically diverse sample of AYAs who are prescribed 6-MP. Third, engagement content can come in and out of vogue very quickly for an AYA population (eg, the shelf

life of popular memes may be short, and high circulation of popular memes may reduce novelty). We vetted and selected content that AYAs liked and perceived as rewarding; however, it is possible that they will become less desirable over time. Fourth, additional tailoring of engagement strategies is likely needed because of individual preferences. Finally, there may be feasibility challenges with an app-based intervention that is dependent on the completion of EMA surveys.

Conclusions

Together, this study will determine the temporal associations between daily contextual factors on 6-MP adherence and explore the proximal impact of various engagement strategies on EMA survey completion. The execution of this protocol represents an important first step toward translating daily, contextual data into personalized and engaging adherence support. Our future JITAI will combine adaptive strategies to promote treatment adherence while concurrently adapting engagement strategies for promoting EMA completion, which may be a generalizable blueprint for improving the impact and reach of other AYA mHealth interventions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Celebrity quotes.
[DOCX File , 24 KB - resprot_v10i10e32789_app1.docx]

Multimedia Appendix 2
Memes.
[DOCX File , 9779 KB - resprot_v10i10e32789_app2.docx]

Multimedia Appendix 3
Altruistic messages.
[DOCX File , 2425 KB - resprot_v10i10e32789_app3.docx]

Multimedia Appendix 4
Animal facts.
[DOCX File , 25 KB - resprot_v10i10e32789_app4.docx]

Multimedia Appendix 5
Peer-reviewer report from National Cancer Institute NCI - Subcommittee J - Career Development (National Institutes of Health).
[PDF File (Adobe PDF File), 168 KB - resprot_v10i10e32789_app5.pdf]

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Abbreviations

6-MP: 6-mercaptopurine
ADAPTS: Adherence Assessments and Personalized Timely Support
AYA: adolescent and young adult

CHOP: Children's Hospital of Philadelphia
EMA: ecological momentary assessment
JITAI: just-in-time adaptive intervention
mHealth: mobile health
REDCap: Research Electronic Data Capture

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Protocol

Efficacy and Safety of Remote Cardiac Rehabilitation in the Recovery Phase of Cardiovascular Diseases: Protocol for a Multicenter, Nonrandomized, Single-Arm, Interventional Trial

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Abstract

Background: Conventional group-based outpatient cardiac rehabilitation through monitoring and center-based approaches for patients in the recovery phase has shown strong evidence for the prevention of cardiovascular diseases. However, there are some cases in which maintaining attendance of center-based cardiac rehabilitation is difficult.

Objective: This study aims to ascertain the safety and efficacy of remote cardiac rehabilitation (RCR) in the recovery phase in patients with cardiovascular disease.

Methods: Patients satisfying the study criteria will be recruited from multiple institutions (approximately 30) across Japan. In total, 75 patients (approximately 2 or 3 patients from each institution) are proposed to be recruited. Patients enrolled in the RCR group will be lent devices necessary for RCR (including calibrated ergometers and tablets). Patients will perform anaerobic exercise at home using ergometer for 30-40 minutes at least 3 times weekly. During exercise, an instructor will monitor the patient in real time (using interactive video tools and monitoring tools for various vital data). Moreover, educational instructions will be given 3 times weekly using e-learning methods.

Results: The primary endpoint is the peak oxygen uptake 2-3 months from the start of exercise or 6-min walk test. The extracted data will be compared between RCR patients and controls without RCR.

Conclusions: The establishment of the system of RCR proposed in this study will lead to the development of more extensive applications, which have been insufficient through conventional interventions.

Trial Registration: University Hospital Medical Information Network—Clinical Trials Registry UMIN–CTR UMIN000042942; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000048983

International Registered Report Identifier (IRRID): DERR1-10.2196/30725

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KEYWORDS

cardiac rehabilitation; remote system; e-learning; exercise capacity; rehabilitation; cardiovascular disease; monitoring system; disease prevention; cardiology

Introduction

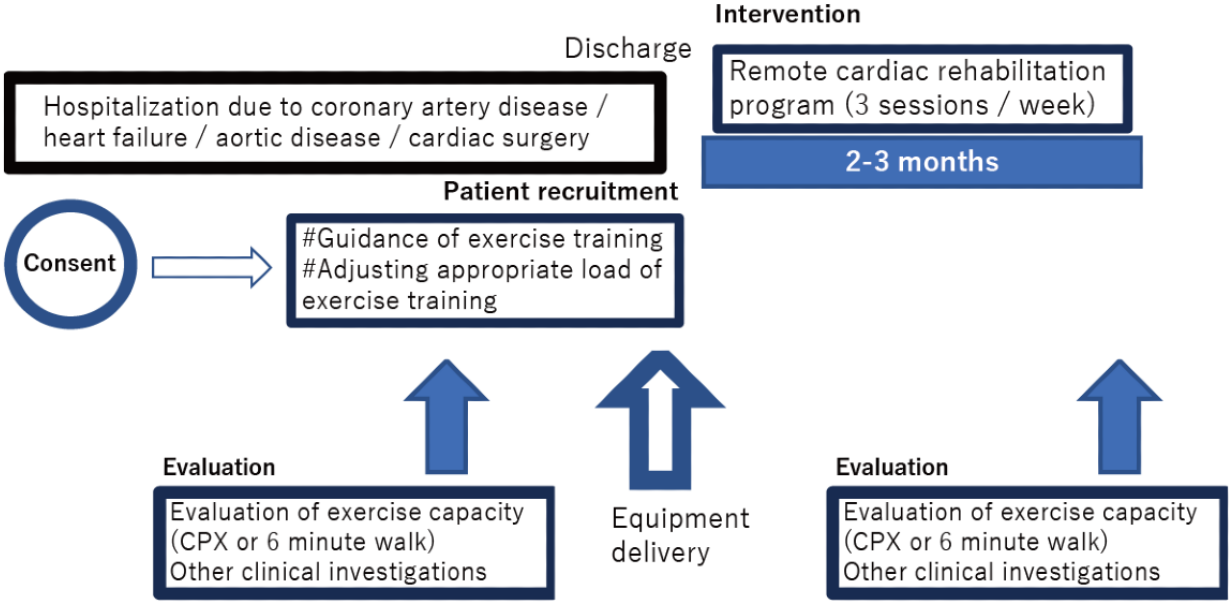
Conventional group-based outpatient cardiac rehabilitation through monitoring and center-based approaches for patients in the recovery phase has shown strong evidence for the prevention of cardiovascular diseases [1-5]. However, maintaining attendance during center-based cardiac rehabilitation is difficult with certain patients because of the distance from their home to rehabilitation sites [5-8]. Poor program adherence is a major issue because the benefits of center-based rehabilitation depend on exercise frequency to a certain extent [9]. Moreover, because of the spread of COVID-19, this form of medical care is expected to present cluster infection–related risks. Thus, nationwide restrictions have been placed on outpatient cardiac rehabilitation (OCR) for patients with cardiovascular diseases in the recovery and maintenance phases [10-12]. Consequently, treatment for patients with high-risk cardiovascular diseases has become insufficient [13]. The suspension of OCR is expected to increase the instances of rehospitalization of patients with acute myocardial infarction and heart failure. Thus, developing alternative modalities to OCR is an urgent challenge. In recent years, reports on the possibility of remote cardiac rehabilitation (RCR) have been filed sporadically overseas [13-15]. RCR consists of health care delivery similar to that of OCR, which corresponds to monitoring during exercise, education, nutritional counseling, and psychological support via telephone and digital platforms. These include the use of artificial intelligence (AI), the Internet of Things, and e-learning technologies in monitoring the vital signs of patients staying at home, simultaneously ensuring levels of safety comparable with those of in-person monitoring by specialists [16,17]. However, since only a few reports have been available, conclusive data on the benefits of RCR are lacking. This study aims to ascertain the safety and efficacy of RCR in the recovery phase among patients with cardiovascular disease. The establishment of the system proposed in this paper will not only help patients transition from OCR to home-based care but also lead to the development of more extensive applications. In fact, the results of this study might provide some suggestions to consider more efficient ways in continued rehabilitation and disease control in the maintenance stage, which have been insufficient with conventional interventions.

Methods

Selection of Patients for the Study

Patients satisfying the following criteria will be recruited from multiple institutions (approximately 30) certified by the Japanese Association of Cardiac Rehabilitation across Japan: (1) patients who are recommended by the attending physician to continue postdischarge cardiac rehabilitation following in-hospital treatment for diseases indicated for cardiac rehabilitation (including ischemic cardiac disease, heart failure, aortic disease, postcardiac surgeries, and peripheral arterial disease) and (2) patients who voluntarily consent to participate in this study with a complete understanding of thorough explanations provided. Conversely, the exclusion criteria are as follows: (1) patients aged under 20 years; (2) those who are deemed unsuitable to participate in this study by the attending physician; (3) those with complications contraindicated for exercise or with high exercise-induced risks (including highly advanced valve stenosis, serious heart failure equivalent to New York Heart Association [NYHA] classification IV, at risk of serious arrhythmia [including ventricular tachycardia], and serious renal/hepatic disease); (4) those with an implanted defibrillator or ventricular assist device; (5) those with reduced cognitive function; (6) those at a terminal disease stage; (7) those at term pregnancy; and (8) those who are determined by a researcher at each institution to be unable to safely undergo RCR (eg, patients living alone). In total, 75 patients (approximately 2 or 3 patients from each institution) are proposed to be recruited. Patient recruitment started in January 2021 and proceeded through March 2021. The study timeline is described in Figure 1.

Figure 1. Schematic representation of the flow of remote cardiac rehabilitation in this study. CPX: Cardiopulmonary exercise test.

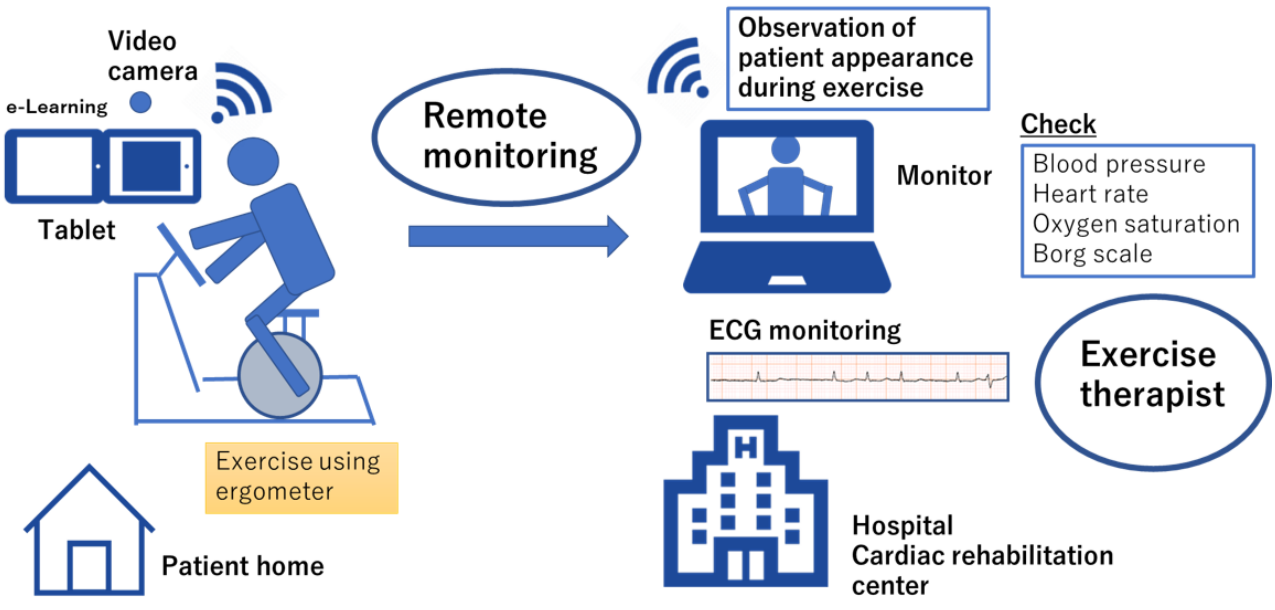


RCR Protocol

This study aims to enroll approximately 75 patients introduced to RCR and compare them with patients who received OCR for the same duration as that for a historical control group. The criteria for the control group are as follows: (1) patients who are recommended by the attending physician that they continue postdischarge rehabilitation following in-hospital treatment for diseases indicated for cardiac rehabilitation and (2) those who took cardiopulmonary exercise testing or a 6-min walk test at 2-3 months after discharge.

Patients enrolled in the RCR group will be lent devices necessary for RCR (including calibrated ergometers and tablets) (Figure 2). The main part of this RCR program will be anaerobic exercise using the lent ergometer. The appropriate exercise intensity in RCR will be determined during hospitalization or after discharge. The intensity levels will be set individually at the anaerobic threshold (AT), for instance, based on the heart rate at the AT, in accordance with the results of cardiopulmonary function testing [18,19]. Alternatively, intensity levels will be determined in reference to the exercise load given during hospitalization. In principle, the duration of exercise will be 30-40 min, starting from ~10 min and then gradually extended. A Borg scale score of 11-13 is the intended target exertion level. The frequency of exercise will be at least 3 times weekly. Upon initial checkup of each exercise session, body temperature, weight, blood pressure, and heart rate are recorded. During exercise, an instructor will monitor the patient in real time (using interactive video tools and monitoring tools for various vital data) and check blood pressure, heart rate, oxygen saturation, and respiratory rate regularly. Data of the electrocardiographic waveform are sent from patients to monitor located at the cardiac rehabilitation center, which could be observed by the instructor. When there are signs or symptoms that suggest that continuing exercise has some risks for worsening a patient's state, the instructor instructs the cessation of that exercise session and, if necessary, the instructor instructs outpatient consultation. At the final checkup, the Borg rating of the perceived exertion scale is checked in addition to data on blood pressure and heart rate. Each patient performs exercise while being given real-time instructions by the instructor via the remote system, thereby guaranteeing safer exercise sessions than conventional methods. During exercise therapy sessions, the patient can video chat with the instructor through the system. Through this system, communication can be performed bidirectionally. The exercise sessions will be carried out on a 1-on-1 basis with the instructor for every patient. No serious complications have been previously reported in exercise therapies with respect to the appropriate exercise prescriptions [20-22]; thus, RCR is possibly safer than exercise performed by individual patients at their discretion. Moreover, educational instructions will be given 3 times weekly through e-learning methods. The e-learning content will include thorough information on the risks of disease, nutrition, lifestyle modification for disease prevention, guided exercise, and medication. Data on patients' understanding of disease control will be collected. The e-learning videos will be made available for watching on tablets or other devices through the internet, using a proprietary app. The video content to be played will be determined by the medical team in accordance with relevance to the risks and diseases pertaining to that particular patient. Finally, to assess the understanding of the content, the patient will be asked to take a mini-test on a tablet. The mini-test is prepared for the content of each e-learning educational material. Subsequent educational programs will be adjusted on the basis of the results obtained. If issues are noted in monitoring devices or transmission issues, we shall stop the exercise session from a safety point of view and make an adjustment in the remote devices to resume subsequent exercise sessions. The clinical study will be conducted strictly in accordance with ethical guidelines and the latest revisions to the Declaration of Helsinki. This clinical trial is registered with the University Hospital Medical Information Network—Clinical Trials Registry (UMIN–CTR; UMIN000042942). Additionally, the protocol has been approved by the institutional review board of Tokyo University Hospital (2020305NI).

Figure 2. Schematic representation of remote cardiac rehabilitation in this study. ECG: electrocardiogram.



Setting of Endpoints

The primary endpoint is the peak oxygen uptake 2-3 months from the start of exercise or 6-min walk test. The secondary endpoints are as follows: indices of cardiopulmonary exercise testing, occurrence rates of clinical events (all-cause deaths, cardiovascular deaths, and cardiovascular hospitalizations), N-terminal fragment of pro–B-type natriuretic peptide (NT-pro BNP) or BNP, health-related quality of life (QOL) scores, daily activity amounts, and questionnaire results. For both groups, various data items will be collected during regular checkups at and 2-3 months after hospital discharge, and improvements in exercise tolerance (peak oxygen intake) will be compared with the occurrence rates of clinical events.

Data Collection

We will also collect the following data upon admission: (1) basic information such as facility name, record date, indications for cardiac rehabilitation, hospitalization date, birthdate, sex, height, weight, and social factors (ie, living alone, living with someone, and institutionalization); (2) patient background, including history of hospitalization for heart failure, underlying heart diseases (ischemic heart disease, heart failure, aortic and peripheral artery disease, valvular disorder, and congenital heart disease), concurrent diseases/complications (hypertension, diabetes, atrial fibrillation, cerebral stroke, peripheral vascular disease, chronic kidney disease, anemia, chronic obstructive pulmonary disease, and smoking); (3) treatment history (before hospitalization), including percutaneous coronary intervention, coronary artery bypass grafting, pacemaker placement, and valve surgery; (4) discharge day; (5) vital data (blood pressure and pulse rate); (6) cardiac disease severity in accordance with NYHA classification; (7) clinical laboratory data, including lymphocyte count, hemoglobin, creatinine, sodium, albumin, total bilirubin, uric acid, and BNP or NT-Pro BNP; (8) imaging data, such as electrocardiography, chest radiography, and echocardiography (including left ventricular end–diastolic diameter, left ventricular end–systolic diameter, left ventricular ejection fraction, interventricular septum width, left ventricular posterior wall width, valve lesions, transmitral flow pattern, mitral annular ring early diastole wave, left atrial volume index, and tricuspid regurgitation maximum blood velocity); (9) 6-min walk test and cardiopulmonary exercise testing; (10) questionnaires, health-related QOL scores, and sarcopenia scores; and (11) prescribed drugs. We will collect the following items 2-3 months after discharge (at an outpatient visit): (1) vital data; (2) NYHA classification; (3) clinical laboratory data; (4) imaging data; (5) 6-min walk test and cardiopulmonary exercise testing; (5) questionnaires, health-related QOL scores, and sarcopenia scores; and (6) prescribed drugs. We will also collect the following items 1 year after discharge (at an outpatient visit): all-cause deaths, cardiovascular-related deaths, and hospitalization due to cardiovascular disease (except for planned hospitalization).

Data Analysis

The analysis will be performed as follows: data on the primary and secondary endpoints of the RCR and control groups will be expressed as mean (SD) or median (quadrant) values. JMP software (SAS Institute) will be used for statistical analysis. Continuous variables will be analyzed using a 2-tailed independent samples *t* test and the Mann–Whitney *U* test. For categorical variables, a chi-square test will be conducted. The RCR group will be compared with the historical control group at the primary and secondary endpoints. The sample size was calculated on the basis of the following estimation. The sample size has been estimated from the data of peak oxygen consumption. A difference in peak oxygen consumption, which is considered clinically relevant, will be in accordance with that reported previously [23,24]. Setting the 2-sided significance level at 5% and power at 80%, a sample size of 67 subjects per group will be required, after allowing for a 40% drop-out rate. Considering these issues, 3 cases are planned to be assigned to each institution (total 75 cases). The level of statistical significance will be set at $P<.05$.

Results

This study was funded in December 2020 and received ethical approval in January 2021, and recruitment began in January 2021. In total, 59 patients have been recruited in the study by March 2021.

Discussion

Aim of This Trial

This trial aims to investigate the efficacy and safety of RCR in the recovery phase for patients with cardiovascular diseases. This RCR protocol includes 2 parts: (1) aerobic training using an ergometer, which will be installed in the patients' homes and (2) patient education using an e-learning system. Safety during patients' exercise will be ensured by monitoring multifaceted parameters such as blood pressure and heart rate, electrocardiography, and observation of patients during exercise through video chats. The e-learning system will promote an increased understanding of cardiovascular diseases.

Strengths and Limitations

This trial is not randomized and observational; thus, background factors may not be accurately aligned with data on the control group, which will be based on clinical records. Results of exercise capacity is considered the primary outcome; however, the evaluation will be based on the 6-min walk test or a cardiopulmonary exercise test because the cardiopulmonary exercise test cannot be performed at all institutions, and some institutions can only measure exercise capacity by evaluating the 6-min walk test. This inconsistency in the evaluation of exercise capacity might decrease the statistical power of this study. Indeed, the compatibility of data between the cardiopulmonary exercise test and 6-min walk test has not been verified [25]. Laboratory data are measured at each facility, using the method prescribed at each facility, possibly resulting in differences in the laboratory data between each facility. Conversely, increasing the versatility of introducing RCR in this study might facilitate the application of the RCR protocol at various facilities.

Potential Implications of This Trial

If this trial successfully confirms the efficacy of RCR, it will provide a valid alternative for patients who cannot participate in group-based outpatient rehabilitation programs because of various reasons. Moreover, the program may be applicable to diseases other than those explored in this study. The development of this modality may help overcome the requirement of recruiting patients in group-based OCR programs. Although this study focused only on cases in the recovery phase, patients in the maintenance phase may enroll under similar regimens. Furthermore, constructing a home rehabilitation environment monitored by a specialist will motivate the patient to manage his/her lifestyle habits and continue exercising. By constructing systems, teaching materials, and software applications for such RCR programs, we will be able to control not only disease prophylaxis/treatment but also lifestyle habits, including diet, sleep, and exercise. Hence, such systems will be utilized in diverse fields ranging from medicine, disease control, and health augmentation. The RCR protocol may provide remote intervention platforms for various health care professionals, including nutritionists, pharmacists, and exercise instructors, and apply to rehabilitation in other diseases (eg, cancer and cerebral infarction).

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Authors' Contributions

HI, EA, TH, SM, and YK conceptualized the study. EA acquired the funding for this study. HI and EA designed the study methodology. HI and EA drafted and edited the manuscript. KN, MS, MT, and IK critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

EA is affiliated with the Department of Therapeutic Strategy for Heart Failure, Graduate School of Medicine, University of Tokyo, which is endowed by NIPRO-Corp, Terumo-Corp, Senko-Medical-Instrument-Mfg, Century-Medical-Inc, ONO-pharmaceutical-Co Ltd, Medtronic-JAPAN Co Ltd, Nippon-Shinyaku Co Ltd, Abiomed-Inc, AQuA-Inc, Fukuda-Denshi Co Ltd, and Sun-Medical-Technology-Research Corp. MS is affiliated with an endowment department sponsored by HIMEDIC Inc and Siemens Healthcare KK. All authors declare that they have no competing interests with the content of this manuscript.

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Abbreviations

AI: artificial intelligence
AT: anaerobic threshold
BNP: B-type natriuretic peptide
NYHA: New York Heart Association
OCR: outpatient cardiac rehabilitation
QOL: quality of life
RCR: remote cardiac rehabilitation

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Protocol

An Early Warning Risk Prediction Tool (RECAP-V1) for Patients Diagnosed With COVID-19: Protocol for a Statistical Analysis Plan

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Abstract

Background: Since the start of the COVID-19 pandemic, efforts have been made to develop early warning risk scores to help clinicians decide which patient is likely to deteriorate and require hospitalization. The RECAP (Remote COVID-19 Assessment in Primary Care) study investigates the predictive risk of hospitalization, deterioration, and death of patients with confirmed COVID-19, based on a set of parameters chosen through a Delphi process performed by clinicians. We aim to use rich data collected remotely through the use of electronic data templates integrated in the electronic health systems of several general practices across the United Kingdom to construct accurate predictive models. The models will be based on preexisting conditions and monitoring data of a patient's clinical parameters (eg, blood oxygen saturation) to make reliable predictions as to the patient's risk of hospital admission, deterioration, and death.

Objective: This statistical analysis plan outlines the statistical methods to build the prediction model to be used in the prioritization of patients in the primary care setting. The statistical analysis plan for the RECAP study includes the development and validation of the RECAP-V1 prediction model as a primary outcome. This prediction model will be adapted as a three-category risk score split into red (high risk), amber (medium risk), and green (low risk) for any patient with suspected COVID-19. The model will predict the risk of deterioration and hospitalization.

Methods: After the data have been collected, we will assess the degree of missingness and use a combination of traditional data imputation using multiple imputation by chained equations, as well as more novel machine-learning approaches to impute the missing data for the final analysis. For predictive model development, we will use multiple logistic regression analyses to construct the model. We aim to recruit a minimum of 1317 patients for model development and validation. We will then externally validate the model on an independent dataset of 1400 patients. The model will also be applied for multiple different datasets to assess both its performance in different patient groups and its applicability for different methods of data collection.

Results: As of May 10, 2021, we have recruited 3732 patients. A further 2088 patients have been recruited through the National Health Service Clinical Assessment Service, and approximately 5000 patients have been recruited through the DoctalyHealth platform.

Conclusions: The methodology for the development of the RECAP-V1 prediction model as well as the risk score will provide clinicians with a statistically robust tool to help prioritize COVID-19 patients.

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KEYWORDS

COVID-19; modeling; remote assessment; risk score; early warning

Introduction

Trial Background and Rationale

Since the start of the pandemic, there has been extensive work [1-3] to develop risk scores for the management of patients with acute COVID-19 that can help to predict the risk of hospitalization, deterioration, and death.

There is pressure on clinical services, and evidence that a small percentage of patients experience precipitous deterioration (usually on about day 7 after symptom onset) [4]. For this reason, there is a growing clinical need to develop and validate an early warning risk tool to be used in a primary care setting that is specific to COVID-19 and based on data that can be reliably collected during a remote consultation.

The RECAP (Remote COVID-19 Assessment in Primary Care) trial (NCT04435041) was designed to develop an early warning tool for patients diagnosed with COVID-19 in primary care settings. The original study protocol [5] outlines the study rationale and data collection process. This paper describes the process for quantitative development and validation of the RECAP-V1 model. The primary objective is to produce a multivariable risk prediction tool to facilitate primary care physicians and other clinicians working in the community in the early identification of COVID-19 patients that are at higher risk of requiring hospital admission, and to inform the early escalation of their treatment, with the aim to expedite admission where necessary and decrease deaths.

To minimize the risk of data selection bias and data-driven interpretation of results, we here outline a prespecified statistical analysis plan (Version 1.0), which details all of the analysis steps to develop and validate the risk prediction model.

Research Questions

We aim to answer the following research questions: (1) What is the optimum risk model for RECAP-V1 to predict hospital admission? (2) What are the sensitivity, specificity, and positive and negative predictive values of the RECAP-V1 risk tool as used in the primary care assessment of COVID-19 patients?

Study Objectives

The primary objective of the study is the development of a data-driven risk tool (RECAP-V1) for use in general practitioner (GP)-patient consultations (mainly by phone or video) in the context of COVID-19. As a secondary objective, the early warning risk tool will be externally validated on an independent dataset. As a third objective, the performance of the model in additional datasets will be assessed. Data for both model development and model validation will be prospectively collected.

Methods

Design

RECAP is a prospective cohort observational study. Data are remotely collected through a questionnaire form outlined in the original study protocol [5] for study-specific data, with additional demographic data being collected through routine electronic health record systems run by participating clinical practices.

Sample Size

Model Development and Internal Validation

Assuming that 10% of patients diagnosed with COVID-19 will be admitted to hospital [6], a 0.05 acceptable difference in apparent and adjusted Cox-Snell R-squared, 0.05 margin of error in estimation of the intercept, a binary outcome based on admission to hospital, and a maximum of 24 predictor parameters [5], we estimate that the minimum sample size required for new model development is 1317 participants enrolled for the development set [7].

External Validation

For assessment of the prediction accuracy of the model, the sample size was calculated based on the assumption that 85% specificity would be the lowest level worth carrying forward because lower values would be considered too low for such a model to be used to make clinical decisions. We focus on specificity, because we are keen for the model to correctly identify the true negatives (and reduce the number of false negatives) considering the risk associated with missing a diagnosis. Based on a 95% CI and precision of 0.05, we aim to recruit at least 1400 patients for model external validation, assuming 87% specificity and a hospitalization rate of 10%.

Assuming a loss to follow-up of 5%-6%, due to possible linkage failure or not recording admission, we aim to recruit at least 2880 participants.

Study Population

The main cohort will include patients presenting with clinically diagnosed COVID-19 in primary care requiring assessment of risk of clinical deterioration.

Eligibility Criteria and Consent

Patients 18 years old and older, being seen (any form of contact, including face-to-face or remote) in a primary care setting where

COVID-19 cases are occurring and running either a practice-based triage system or a COVID-19 remote monitoring service such as National Health Service (NHS)111 COVID-19 Clinical Assessment Service (CCAS) or a local equivalent, are enrolled in the study.

Patients being seen in practices not using a compatible electronic record system or using a remote monitoring system that cannot provide an output that is at least mapped to the appropriate Systemized Nomenclature of Medicine (SNOMED) concepts are excluded.

Patients locally record as being willing and able to provide informed consent for data linkage either at a GP contact (entered on a template) or as part of a "platform service" (checked by the patient on a template or via chatbot). If consent to data linkage cannot be obtained, an opt out will be provided and linkage sought under the Control of Patient Information provisions [8].

Population Data

The data are collected in four different systems: (1) iCare (North West London Whole Systems Integrated Care), which is the Imperial analytics platform for high-paced processing of patient data from North West London practices; (2) the Royal College of General Practitioners (RCGP) Research and Surveillance network (RSC Practice network), which is a general practice sentinel network that collects data from practices across England and Wales; (3) NHS111 CCAS; and (4) DoctalyHealth Care, a home monitoring service for patients with a diagnosis of COVID-19.

The data will be collected using templates embedded in health record systems used in routine contacts for patients with suspected COVID-19, and then the records will be linked between primary and secondary care. The consent for this data linkage will also be collected. Once recruited, patients will be followed up for 28 days after the COVID-19 diagnosis.

Definition of Analysis Population

The primary population set is patients presenting with clinically diagnosed COVID-19 in general practices and requiring assessment for the risk of clinical deterioration. The primary RECAP-V1 model will be built using data from iCare and externally validated using data from the RSC Practice network. Additional population sets are patients that are part of DoctalyHealth, as well as patients who are being assessed by the NHS111 CCAS. Based on clinical expertise, the patients who are being assessed as part of NHS111 CCAS are expected to be experiencing more severe symptoms of COVID-19. Similarly, for DoctalyHealth, the data are collected from a home monitoring system; hence, we are expecting this patient population to be different from the iCare and RSC Practice network populations. Moreover, some of the important clinical parameters such as oxygen saturation or rate of breathing may be missing for DoctalyHealth.

A separate RECAP model will be built for the CCAS patients and the DoctalyHealth patients.

Model Outcome Variable

The outcome variable considered in building the risk model RECAP-V1 is hospitalization within 28 days following a positive ascertained diagnosis of COVID-19 (either a clinical diagnosis or a polymerase chain reaction test).

Hospitalization is defined as a patient being admitted and having spent at least one night in a bed in a hospital in the period following a COVID-19 diagnosis and up to 28 days following the diagnosis.

Model Predictor Variables

The predictor variables to be included as candidates for the model have been decided through a Delphi process by the investigators and the research team, which are presented in Figure 1. The SNOMED codes are also outlined for these predictors. These predictor variables are contained in RECAP V0 [9], which include patients' sociodemographic information (eg, age, ethnicity, adverse social circumstances) and comorbidities. The predictors that will be included in the primary model are continuous (heart rate, respiratory rate, trajectory of breathlessness, oxygen saturation at rest, oxygen saturation after 40 steps, temperature, time from first symptom [days], age, BMI) and categorical variables (profound tiredness or fatigue, muscle aches, myalgia, cognitive decline, being on a COVID-19 shielded list [10], gender, ethnicity, diabetes, hypertension, coronary heart disease, chronic kidney disease, and adverse social circumstance).

Figure 1. RECAP-V1 model predictor variables and their clinical severity, adapted from Greenhalgh et al [11]. O/E: on examination; ORCHID: Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub; RECAP: Remote COVID-19 Assessment in Primary Care; SNOMED: Systemized Nomenclature of Medicine.

	Variable	Clinical severity			
1	Heart rate (per minute) 78564009 | Heart rate measured at systemic artery (observable entity)	51-90	41-50 or 91-110 or missing data	111-130	≤ 40 OR > 130, if unexplained
2a	Shortness of breath	Not breathless at all 161938003 | No breathlessness (situation)	Breathless on moderate exertion e.g. walking room to room 161939006 | Breathless - moderate exertion (finding)	Breathless on mild exertion e.g. getting out of a chair 161940008 | Breathless - mild exertion (finding)	Severe breathing difficulty; O/E Respiratory distress | 162892000 Can't complete sentences at rest 713661000 | Able to complete sentence in one breath 407588003 | Unable to complete a sentence in one breath
2b	or Respiratory rate (per minute) 86290005 | Respiratory rate (observable entity)	12-20	21-24	9-11 or 25-29	8 or less, or 30 or more
3	Trajectory of breathlessness	Same or better than yesterday 268910001 | Patient condition improved | 359748005 | Patient condition the same	Breathless, worse than yesterday 275723000 | Patient's condition deteriorating (finding)		Significant deterioration in last hour Use 162471005 | Symptom very severe (finding) |
4a	Oxygen saturation at rest 866661000000106 | Peripheral blood oxygen saturation on room air at rest (observable entity)	96% or above	95%	94%	93% or below
4b	or Saturation after 40 steps 866681000000102 | Peripheral blood oxygen saturation on room air on exertion (observable entity)	Fall of 0-1%		Fall of 2%	Fall of 3% or more
4c	or Profound tiredness or fatigue	None or mild 161869003 | Not tired	Noticeably more tired doing usual activities 84229001 | Fatigue	Struggling to get out of bed 301663005 | Unable to get on and off a bed	
5a	Temperature 703421000 | Temperature (observable entity)	≤ 38 °C	38.1-39 °C	> 39 °C or < 35 °C	
5b	or Feeling feverish with shivers	None 161851007 | No temperature	Feverish or chills 373904004 | Feeling hot	Uncontrollable shivering 248457000 | Rigor (symptom)	
6	Time from first symptom (days) Record as 520191000000103 | Date of onset of symptoms (observable entity)	7 or fewer	8 or more	-	
7	Muscle aches 68962001 | Myalgia	None or mild			
8	Cognitive decline	No 248234008 | Mentally alert	Less mentally alert than usual 40917007 | Clouded consciousness	New and worsening confusion 130987000 | Acute confusion	Reduced level of consciousness 417473004 | On examination - decreased level of consciousness (finding) |
9	On COVID-19 shielded list 1300561000000107 | High risk category for developing complication from coronavirus disease caused by severe acute respiratory syndrome coronavirus infection (finding) | For low or moderate risk patients [10] 1300571000000100 | Moderate risk category for developing complication from coronavirus disease caused by severe acute respiratory syndrome coronavirus infection (finding)	No	Yes	-	-

	Demographic factor	Concept ID
1	Age, 65 or over	424144002 | Current chronological age (observable entity) |
2	BMI, > 35	60621009 | Body mass index (observable entity) |
3	Sex, male	184100006 | Patient sex (observable entity) |
4	Ethnicity, non-white	186034007 | Ethnicity / related nationality data (observable entity) |
5	Diabetes	Described by the SNOMED code phenotype within ORCHID
6	Hypertension	Described by the SNOMED code phenotype within ORCHID
7	Coronary heart disease	Described by the SNOMED code phenotype within ORCHID
8	Chronic kidney disease	Described by the SNOMED code phenotype within ORCHID
9	Adverse social circumstances	Described by the SNOMED code phenotype within ORCHID

Statistical Methods

Baseline Demographics

Patient characteristics will be summarized. Summaries of continuous variables will be presented as means (SD) if normally distributed and as medians (IQR) for skewed data; categorical variables will be presented as frequencies and percentages. Baseline demographics will include all of the RECAP V0 variables outlined in Figure 1.

Objective 1 (Primary Objective): Development, Internal Validation, and Identification of Clinical Cut-Off Points of the RECAP-V1 Model

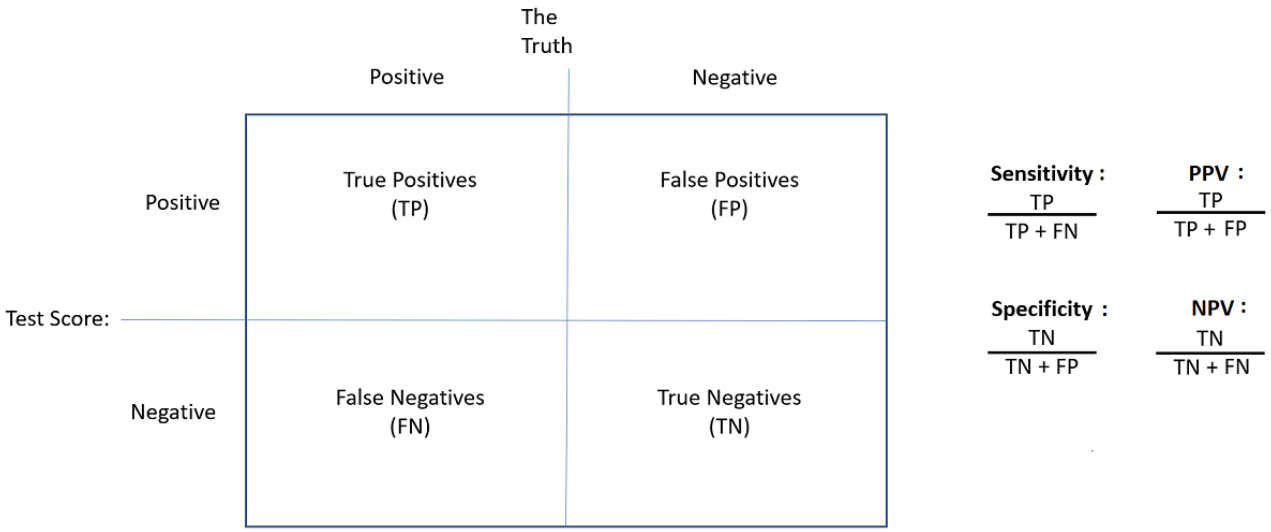
The primary objective of the study is to develop a predictive model based on a logistic regression of the predictive parameters using data from the iCare system. The model will be internally validated by bootstrapping the dataset. Following the internal validation, two cut-off points will be used as separators for red, amber, and green risk of a particular outcome with associated interval likelihood ratios (LRs).

A probabilistic risk prediction based on a multivariable logistic regression model, including the variables in Figure 1 as factors, will be performed on the patients from the iCare dataset, with continuous predictors being treated as fractional polynomials to reflect the potential nonlinearity of the variables. The model will allow estimation of the likelihood of a particular patient being admitted to hospital within 28 days of a COVID-19 diagnosis (primary patient outcome). Some of the variables will be checked for independence from each other by including interaction terms in the model. We will test interactions between BMI and respiratory rate (or shortness of breath if respiratory rate is not collected), age and respiratory rate (or shortness of breath), and coronary heart disease and respiratory rate (or shortness of breath).

The significance of each factor in the list of predictor parameters from Figure 1 will be investigated using a backward elimination regression model, where a multivariable regression model is constructed in the first instance including all of the parameters from the list in Figure 1 and their performance assessed to check for significance. Subsequently, a model using only the predictor factors that were found to be statistically significant ($P<.05$) for the prediction of results will be run.

The final model will then be used to estimate the predicted risk for each patient in the iCare dataset. Based on this continuous risk, the specificity and the sensitivity will be calculated based on the formulas shown in Figure 2. All analyses will be completed after the last patient's final follow-up.

Figure 2. Sensitivity and specificity calculations based on test risk prediction and the real outcome, along with the positive and negative predictive value formulas. NPV: Negative Predictive Value; PPV: Positive Predictive Value.



Model Internal Validation and Evaluation

The model will be validated internally by bootstrapping to ensure it performs well. The goodness of fit of the model will be assessed using the area under the receiver operating characteristic (ROC) curve and optimism-corrected smoothed calibration curves [12] to determine the performance of the model in predicting outcomes in the bootstrapped cohorts, with the final relationship between the predicted and the observed data being expressed as the McFadden R^2 value [13].

To provide better representation of model fit, calibration and discrimination will be performed to better evaluate the accuracy of the model. Calibration of the model will be achieved using Loess-smoothed calibration plots as described above. For the purpose of analyzing discrimination, the data will be stratified by age (65 years old as a cut-off point) and gender. Hence, the model will be tested in population subgroups with age and gender for the subgroup definition. Brier scores will be used to measure the accuracy of the predictions of the model [14].

For each patient in this set, the result of the RECAP-V1 model will be calculated, and an ROC curve will be plotted from the highest to lowest values to determine the cut-off points for the predicted risk that optimize the specificity and sensitivity of the predictor model for red, amber, and green risk groups. The risk groups represent the relative risk of a particular patient outcome, with green signifying a very low risk, amber being a moderate to high risk, and red being a very high risk. This stratification ensures that there is a minimal number of false negatives in the final model and patients are not considered to be at low risk unless absolutely certain. The rate of increase and the point of inflection for the ROC curve will be used to inform the two cut-off points at the green/amber and amber/red points, which will be used as thresholds. The choice of optimum cut-off points is a clinical decision based on the shape of the resulting ROC curve (eg, how well-behaved the curve is, whether it is

asymmetrical). Cut-off points should be clinically informative (ie, have a gradient representing the interval LR that is either greater than 2 or less than 0.5 so that the score changes the prior probability sufficiently). With a two cut-off point score for the red/amber/green (admit/monitor/advise) categories, the red/amber cut-off point should be in the steepest part of the curve (the most abnormal scores) where the LR will increase the risk of admission, and the amber/green cut-off point should be in the shallow part of the curve (the least abnormal scores) where the LR will decrease risk of admission. The ROC curve will thus be divided into three parts from the most abnormal to the least abnormal with three associated interval LRs; we will aim to allocate scores based on maximizing the "most abnormal" interval LR and minimizing the "least abnormal" interval LR with the middle interval LR likely to be around 1. There are several statistical tools for finding these points; however, in our opinion, selecting appropriate points from inspection of the ROC has the highest clinical validity [15].

Objective 2: External Validation of the Model

The model accuracy will then be assessed externally using the RSC Practice network data to verify the specificity of the model predictions, as well as the sensitivity, negative predictive value, and positive predictive value [16,17].

Objective 3: Analysis of Additional Datasets

A separate RECAP-V1 model will be developed, using the same methodology as described in Objective 1, for the CCAS and DoctalyHealth datasets, and the models will be internally validated following the same procedure as used in building the model for the iCare dataset.

Subgroup Analysis

The performance of the model will be investigated in specific groups of patients, focusing primarily on gender and age (<65 years).

Missing Data

The extent of missing data for each variable (outcome and predictors) will be assessed among all patients. Particular note will be taken of the potential for missing data in the oxygen saturation and temperature fields (in case the patient does not have instruments to measure these), and for respiratory rate (difficult to estimate unless independently counted visually) as these are considered particularly important factors for outcome.

If model outcome data are missing for >5% of the patients, methods to deal with missing data will be used and a sensitivity analysis to estimate the effect of using these methods will be carried out by comparing the estimated risk obtained without implementing a missing data method and the risk estimated using missing data methods.

The degree of missingness in predictor variables will be assessed. If the degree of missingness is above 50% for any predictor variable, then that predictor variable will be excluded from the model. If the degree of missingness is less than 50%, the data will be imputed using multiple imputation chain equations [18]. A total of 5 imputations will be performed and aggregated based on Rubin's rules [19].

Data missingness mechanisms will be investigated to ascertain if the data are missing completely at random, at random, or not at random. This will be performed by considering the data structure to understand the dependency relationships between the missing data and the observed data. The missing data will then be described in relation to the degrees of missingness, missing data patterns, and possible reasons for missingness. We will also compare the characteristics of the patients with missing data and patients with complete data entries, which will allow us to assess the plausibility of the data missing completely at random. The distributions of the continuous predictor variables will be investigated for normality. Any missing continuous data that are not distributed normally will be transformed to a normal distribution for imputation and transformed back to the original scale for the final analysis.

Multiple imputation chain equations [18,20] will be used, and all of the predictor variables (with less than 50% missing data) will be included in the imputation model. Variables without missing data will also be included, and the outcome variable (hospital admission) will be used for imputation of the predictor variables. We will use linear regression for continuous variables (normally distributed or transformed), and logit or ordinal logit regression for categorical variables. We will compare observed and imputed values, especially for variables for which the fraction of missing data is large [21].

The same imputation methods will be used in all datasets, for both continuous and categorical variables.

Exploratory Analyses

We are planning to conduct exploratory analyses given the unique data collected in the study.

A time to event data model will be constructed using Cox regression of time to hospital admission. The model will be analyzed as time-series survival data by fitting a subdistribution hazard model [22] to account for deaths from any other causes that generate censored data in the results. This will be achieved by taking the time to admission for each patient. The discrimination of the models will be assessed using the Harrell C and Somer D statistics to measure the association of the ordinal logistic regressions.

A set of alternative risk estimates will also be explored in the possible scenarios for which temperature measurement, oxygen saturation at rest or on exercise, or respiratory rate are missing. It is expected that temperature, oxygen saturation, and respiratory rate might be at high risk of missingness, as in practice these factors might be hard to record. Hence, we will develop a prediction model in the case that these data are missing completely. This will also allow us to investigate the importance of these data for prediction of the risk of hospital admission.

A prediction model will be built using machine learning (ML). We will use nonlinear classifiers, including random forest and gradient tree boost algorithms, as well as a recurrent neural network to build a predictive model based on time-series data, as we expect there may be a nonlinear relationship between the predictors and the discrete outcomes. We will use 10-fold cross-validation with hyperparameter tuning by a grid search.

RECAP-V1 built using logistic regression and the prediction models built using ML will be compared based on diagnostic accuracy estimates. ML methods for missing data imputation will also be applied. For this purpose, we will use random forest–based algorithms, DataWig, and generative models (generative adversarial networks), which have been shown to be superior to traditional missing data imputation techniques [23-25]. These ML methods will be compared to traditional missing data imputation.

Mortality and admission to the intensive care unit (ICU) will also be modeled. Two definitions of death from COVID-19 will be used: (1) death as a result of severe COVID-19 or COVID-19 complications in a hospital setting, and within 28 days of illness onset; and (2) death in a different setting (either after hospital discharge or in patients that were not admitted) within 28 days of illness onset, where COVID-19 is mentioned as a contributor in the death certificate of the patient. We will investigate the number of events for death and admission to the ICU, and determine if we have sufficient power to build predictive models for death and admission to the ICU.

Finally, we will explore combining the CCAS dataset to the primary iCare dataset to increase the power of the model. Differences in the patients between the datasets will be quantified, as well as exploring the effect that adding this additional dataset to the model would have on the performance of the model through internal-external cross-validation stratified for which dataset the patients' data originated to ensure the transferability of the predictions for different subpopulations [16,26,27].

Software

Analyses will be performed using R studio 4.0 and STATA 15. The main R packages used for the analysis will be: rms, mice, miceMNAR, xplorerr, tidyverse, ggplot2, pubh, r2mlm, dplyr, tidyr, plotly, mlr3, and data.table.

Results

A total of 173 active primary care practices have enrolled for the recruitment of patients across the iCare and RSC practice network. As of May 10, 2021, the study has recruited a combined sample of 3732 participants for the development, validation, and accuracy assessment of the model. A total of 2429 participants have been recruited from North West London GP practices (iCare), including the primary care data on the patients' signs and symptoms during the full 28-day follow-up period; 1303 patients have been recruited from RSC practices, similarly recording the signs and symptoms of patients over the full 28-day follow-up period.

Through the DoctalyHealth platform, data have been collected using a remote monitoring system to record the patients' clinical parameters, as well as signs and symptoms. The dataset comprises approximately 5000 patients and will be used to develop a model for this patient set. Additionally, 2088 patients have been recruited through NHS111 CCAS.

The final results of the model development and validation will be reported following the TRIPOD guideline [28] for prediction model development and validation. This study is expected to conclude in December 2021.

Discussion

We have outlined the plan of analysis and methods for building a reliable data-driven early warning risk prediction tool, RECAP-V1, to be used in primary care.

COVID-19 has had a profound impact on the UK health care system, with limited numbers of ventilators and ICU beds. Thus, a method of early identification for not only the patients most at risk based on their demographic data, but also based on their disease symptoms and progression is of vital importance to efficiently treat the patients that need it the most. Previous early warning risk scores that were developed for the flu or generic infectious respiratory disease may not be entirely transferable to COVID-19, further highlighting the need for a reliable and data-driven risk prediction tool to help ensure the best outcomes for the highest risk groups.

Our RECAP-V1 early warning risk score will provide a robust, statistically supported metric for quickly assessing a patient's current risk of hospitalization, and thus help clinicians decide if any change in treatment or closer observation would be warranted.

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Conflicts of Interest

Simon de Lusignan is the Director of the Royal College of General Practitioners Research and Surveillance Centre. He has also received a grant through his university from AstraZeneca for vaccine effectiveness and to explore adverse events of interest. All other authors declare no conflicts of interest.

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Abbreviations

CCAS: COVID-19 Clinical Assessment Service
GP: general practitioner
ICU: intensive care unit
LR: likelihood ratio
ML: machine learning
NHS: National Health Service
RCGP: Royal College of General Practitioners
RECAP: Remote COVID-19 Assessment in Primary Care
ROC: receiver operating characteristic
SNOMED: Systemized Nomenclature of Medicine

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Protocol

Accelerating the Appropriate Adoption of Artificial Intelligence in Health Care: Protocol for a Multistepped Approach

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Abstract

Background: Significant investments and advances in health care technologies and practices have created a need for digital and data-literate health care providers. Artificial intelligence (AI) algorithms transform the analysis, diagnosis, and treatment of medical conditions. Complex and massive data sets are informing significant health care decisions and clinical practices. The ability to read, manage, and interpret large data sets to provide data-driven care and to protect patient privacy are increasingly critical skills for today's health care providers.

Objective: The aim of this study is to accelerate the appropriate adoption of data-driven and AI-enhanced care by focusing on the mindsets, skillsets, and toolsets of point-of-care health providers and their leaders in the health system.

Methods: To accelerate the adoption of AI and the need for organizational change at a national level, our multistepped approach includes creating awareness and capacity building, learning through innovation and adoption, developing appropriate and strategic partnerships, and building effective knowledge exchange initiatives. Education interventions designed to adapt knowledge to the local context and address any challenges to knowledge use include engagement activities to increase awareness, educational curricula for health care providers and leaders, and the development of a coaching and practice-based innovation hub. Framed by the Knowledge-to-Action framework, we are currently in the knowledge creation stage to inform the curricula for each deliverable. An environmental scan and scoping review were conducted to understand the current state of AI education programs as reported in the academic literature.

Results: The environmental scan identified 24 AI-accredited programs specific to health providers, of which 11 were from the United States, 6 from Canada, 4 from the United Kingdom, and 3 from Asian countries. The most common curriculum topics across the environmental scan and scoping review included AI fundamentals, applications of AI, applied machine learning in health care, ethics, data science, and challenges to and opportunities for using AI.

Conclusions: Technologies are advancing more rapidly than organizations, and professionals can adopt and adapt to them. To help shape AI practices, health care providers must have the skills and abilities to initiate change and shape the future of their discipline and practices for advancing high-quality care within the digital ecosystem.

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KEYWORDS

artificial intelligence; health care providers; education; learning; patient care; adoption; mHealth

Introduction

Background

The convergence of information technology and medicine in our dynamic digital era has produced novel applicable solutions for clinical practice [1]. Health care is at an important turning point for the efficient and safe use of artificial intelligence (AI) technologies to transform the quality of care delivered [2]. AI is an expansive term for various systems or technologies that originate from the branch of computer science. Such technologies are designed to emulate and augment human intelligence under headings, such as visual perception, reasoning, learning, speech recognition, and the ability to perform human tasks [3-5]. Machine learning is a subset of AI that depends on algorithms to enable computers to learn patterns and rules by using previous examples [4,6]. AI can be leveraged to help deliver precision medicine, optimize patient and clinical outcomes, reduce costs, and enhance the efficiency and accessibility of the health care system [2]. Despite great technological advances, little is known about how to put this new knowledge and these new tools into practice.

There is emerging evidence that AI has the power to transform care delivery in many domains [7], and recent advancements and breakthroughs in machine learning techniques involving deep neural networks trained on big data have increased the adoption of AI in health care [8]. The extent to which AI technologies could alter the landscape of prevention, diagnosis, medical care, and predictive health services is significant, as well as improve the delivery and effectiveness of health care [9]. AI can play a significant role in this process, given the potential to recognize subtle disease-specific patterns from various sources that humans would never recognize [10]. For instance, AI is currently being used to reduce false-positive results in screening for breast cancer, to revolutionize clinicians' workflow and robotic surgery, and to predict mortality rates of patients [10]. A study by Google Health demonstrated AI's ability to perform better than human experts in breast cancer prediction [11]. Consequently, implementation of this AI system may influence recall rates, the number of unnecessary biopsies, and earlier detection of cancer due to the specificity and sensitivity improvements in identifying invasive cancers. The era of AI envisages new roles of care providers; thus, health professional education and clinical practice will experience profound change. [12].

The implementation of AI is perceived favourably, even enthusiastically by patients due to the possibility of greater engagement and personalized treatment. However, it is often encountered with trepidation from health care providers who are not prepared for such an evolution of practice [5,13]. According to Briganti and Le Moine, this trepidation can be attributed to four widely discussed reasons [13]. First, owing to the lack of education in AI, health care providers may feel unprepared to adopt AI in their clinical settings [13]. Second, there is an increased administrative burden associated with a shift in the emergence of technologies being used to support healthcare processes such as electronic health records (EHRs). This can contribute to clinician burnout [13]. Third, many clinicians fear that these new tools will replace their roles, even though emerging academic literature highlights that AI will be used in conjunction to support clinicians in making decisions [13]. Finally, it is imperative to note that the current legal structure does not specify the terms of liability in the event of adoption or rejection of algorithm recommendation, which can leave the care provider exposed to potential legal outcomes [13].

There are numerous barriers in understanding the potential of AI in health care ecosystems [2]. Current challenges are centered on the application of AI to populations not depicted in the training and testing of data sets, use of biased data for the development of AI models, neglect toward the potential inadvertent consequences of care, and lack of data regarding the efficacy and effect on patient outcomes and the health care system [2]. The *black box* phenomenon encumbers the adoption of AI among the medical community because they ultimately have to make the final clinical decision without understanding of how the variables within the AI algorithm forms the prediction, in which their decision is based on [10]. Thus, it is difficult for clinicians to trust the algorithm, and in turn, become accustom to working with AI [10]. Health care providers should leverage technology [14] and advocate for the ethical use of patient data and AI to maintain trust with their patients and enhanced, equitable care [15]. As the health care community prepares for this shift with a sustained commitment to upholding high standards of care, it is crucial to refocus medical education on developing medical innovators [16].

The emergence of AI offers unprecedented opportunities for accelerating scientific advances in health care; however, current educational structures are not sufficient to prepare care providers to leverage those opportunities. Health care providers often face deficits in the knowledge and skills needed to provide optimal care for all patients [17]. Lifelong learning has been defined in the literature as the sustained motivation to pursue self-initiated learning activities and having the required information-seeking skills, and the ability to identify one's own learning needs [18]. The literature on implementing health information systems (HISs) indicated that adequate education efforts had a favorable impact on clinicians' views on HIS adoption and their ongoing use of the system [19,20]. A study by Bredfeldt et al [20] highlighted that education was associated with increased use of key EHR features for medication list management, an addition to the meaningful use criteria. Similarly, Kraus et al [19] reported that physician adoption with HIS reached 40% in the

first month and stabilized at 75% within a year. The authors asserted that ensuring success requires a systematic approach to change management, including training, workflow redesign, and support during the transition [19]. Embedding AI concepts as part of knowledge translation could be a fundamental step in equipping care providers to engage in competent and safe practices [4]. Chaumunyonga [4] asserted the importance of equipping radiation therapy professionals with the knowledge and skills to participate in discussions about the use of AI and integrate AI in their practice where quality and safety standards are maintained. Given the importance and potential impact of AI, knowledge translation products should include content that will allow care providers to translate knowledge of emerging technologies into their own practice [21]. Sit and colleagues reported that it is vital to seize this opportunity to prepare a health care workforce with adequate knowledge and skills to effectively use new digital tools, including AI technologies [22]. The curricula should be reformed to meet the needs of the changing health care system [23].

Objective

The objective of this project is to accelerate the appropriate adoption of data-driven and AI-enhanced care by focusing on the mindsets, skillsets, and toolsets of point-of-care health providers and their leaders in the health system.

Specifically, we aim to (1) develop and evaluate knowledge translation interventions to harness data and AI to enhance and optimize health care delivery, (2) examine the contextual factors that influence the success of the program and the adoption of AI initiatives in health care, and (3) explore the barriers to and facilitators of the implementation of an AI education program.

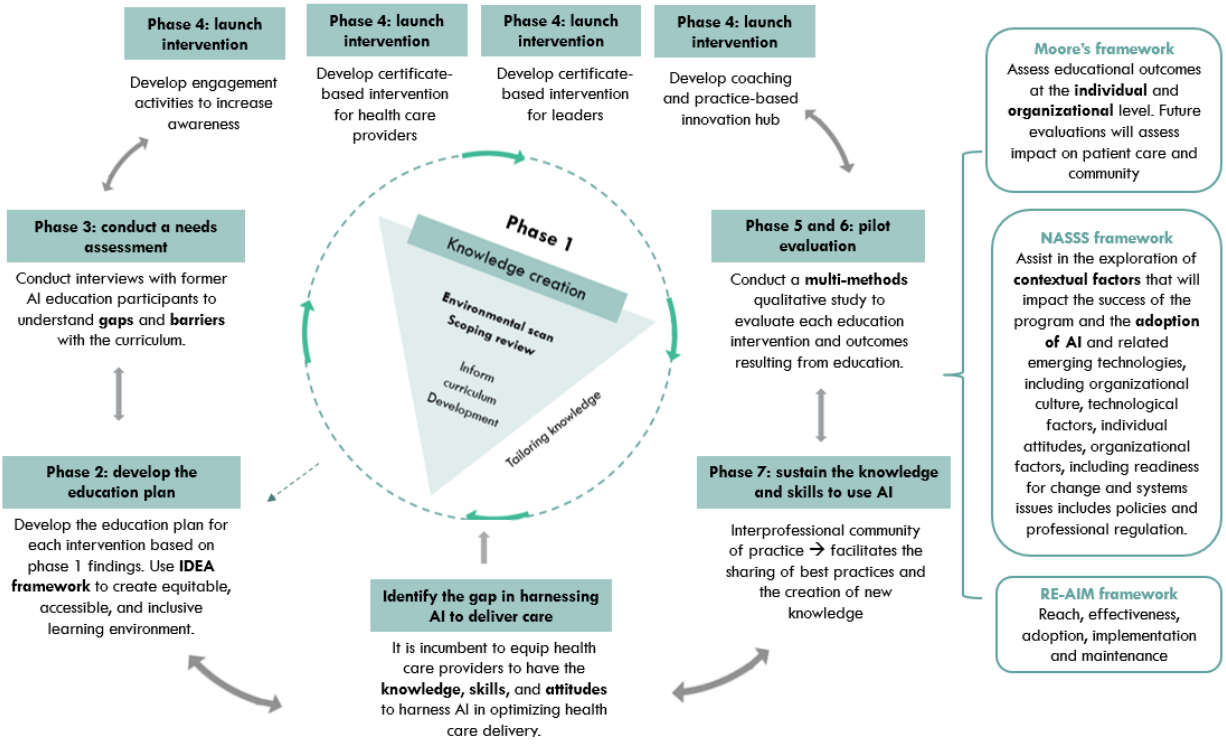
Methods

Overall Study Design

In taking an integrative knowledge translation approach, this project will be framed by the Knowledge-to-Action (KTA) framework [24,25] for transformational change in the health care system through the integration and developmental evaluation of evidence-based AI education interventions (Figure 1).

The knowledge funnel represents the refinement of the knowledge base to inform the knowledge product development, whereby first the knowledge is created, then synthesized and interpreted [26]. Knowledge synthesis involves the identification, appraisal, and aggregation of studies or information relevant to the research questions [26]. The action part of the process is represented by the outer circle, which consists of activities leading to the effective implementation of knowledge [26].

Figure 1. Overall study design adapted from the study by Graham et al [26] with permission. AI: artificial intelligence; IDEA: inclusion, diversity, equity, and accessibility framework; NASSS: Nonadoption, Abandonment, and Challenges to Scale-up, Spread, and Sustainability.



Evaluation Approach

The research will examine the knowledge uptake and barriers to AI adoption in clinical settings using quantitative and qualitative methodologies. Table 1 illustrates the frameworks used in each phase as part of the evaluation process.

A logic model was developed to describe the intervention design and guide the evaluation plan (Figure 2). The activities and outputs mentioned in the logic model were expanded in each phase of the KTA framework.

Table 1. Cocreating the knowledge translation method.

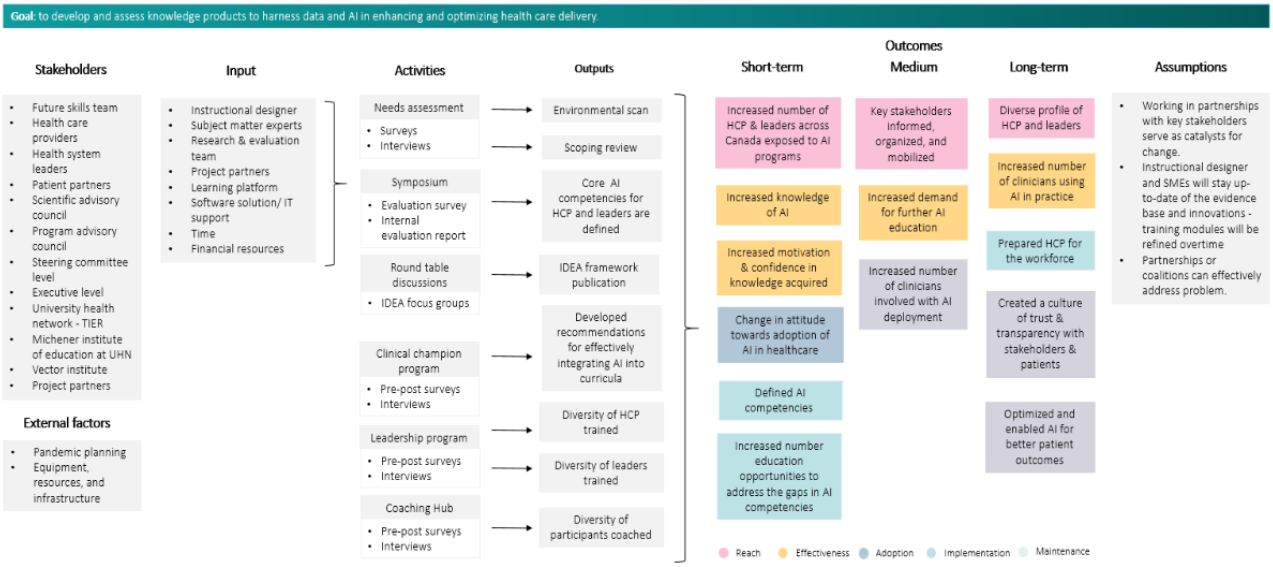
Knowledge translation phase	Aim 1 (Moore framework)	Aim 2 (NASSS[a] framework)	Aim 3 (RE-AIM[b] framework)
Phase 1: identify the problem	✓[c]		
Phase 2: adapt to the knowledge			✓
Phase 3: assess barriers and facilitators			✓
Phase 4: launch the intervention	✓	✓	
Phases 5 and 6: pilot evaluation	✓	✓	✓
Phase 7: sustain ongoing knowledge use		✓	✓

[a]NASSS: Nonadoption, Abandonment, and Challenges to Scale-up, Spread, and Sustainability.

[b]RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

[c]Phase to be evaluated.

Figure 2. Logic model. AI: artificial intelligence; HCP: health care provider; IDEA: inclusion, diversity, equity, and accessibility framework; IT: information technology; SME: subject matter expert; TIER: The Institution for Education Research; UHN: University Health Network.



Phase 1: Identify the Problem and Create Knowledge

In this first phase, our aim is to identify the problem and the knowledge required to address this gap. The health care ecosystem is witnessing a surge in AI-powered digital health technologies that can potentially augment the delivery of care and affect population health [27]. Although the advent of data technologies has led to numerous opportunities to transform the evolving arenas of care, organizations are much slower in embracing technological changes [28,29]. Brinker summarized this concept of technologies changing exponentially as organizations change logarithmically, which is known as the Martec law [28,29]. This discrepancy can lead to a widening gap in how organizations and care providers can harness the potential of AI technologies to enhance practice and care delivery [28,29]. To address this gap, Brinker suggests that health care organizations must address how those technologies will be integrated into the operations and culture of an organization [29]. This point was reinforced in the review by Topol [7], who reported that an effective culture of learning is needed to enable the workforce to reframe their knowledge and become digitally competent and confident within an increasingly technology-driven environment. The interventions we develop will not only increase knowledge, but also provide a multidisciplinary audience with the required tools to lead conversations around shifts in practice, policy, procedures, and problem-solving approaches that optimize this new digital presence.

An evidence-based education and coaching program will be developed for health care professionals to build the knowledge, skills, and capabilities to translate the potential power of AI applications into effective practice. First, we will plan, develop, and scale education interventions designed to create awareness and change mindsets regarding the appropriate use and applications of AI. The shift in mindset will explore equity, social responsibility, advocacy, data governance, and transparency for AI use. Second, we will build advanced AI literacy skills for care providers and leaders by providing access to high-quality education interventions that build the capability for augmented intelligence through AI. Finally, a coaching and practice-based innovation hub will be implemented to support practice change and build self-efficacy to use AI in practice. These educational interventions will be built on what is learned through an environmental scan, scoping review, and a needs

assessment, all of which will inform curricular content, delivery and implementation approaches, and programming outcomes.

Phase 2: Adapt Knowledge

In this second phase, our aim will be to ensure that we adapt the knowledge to the local context and consider strategies that help to design and develop equitable, diverse, and inclusive knowledge translation products. The increasing adoption of AI tools in the past decade presents an opportunity for a paradigm shift in health care toward economical, integrated, and equitable care delivery [27]. This shift can be seen through the lens of the National Academy of Medicine Quintuple Aim, focusing on various domains of health care improvement and equity. There are opportunities to build and focus on AI to reduce cost and improve population health, care team well-being, patient experience, and equity and inclusion [27]. The affordability of remote monitoring devices increased web-based care, and real time feedback tools position AI as an essential factor in achieving the quintuple aim of health care [27]. The authors further emphasized the need for significant retooling of the health workforce and the required shifts in entry to practice [27]. The National Academy of Medicine places a particular focus on mitigating the risk that AI might lead to a less equitable delivery of services, and we will follow its recommendations on education for AI-enabled equity and diversity [27]. Specifically, the framework will be used to guide the implementation and evaluation of AI through an equity and diversity lens, evaluating data biases, trust and transparency factors, and the inclusion of the social determinants of health. With a focus on diversity and equity as key principles in the study design, the evidence generated through this initiative will be applicable to many settings and will inform evidence-based approaches to the adoption of AI in other industries critical to the promotion of health and better outcomes.

To ensure meaningful and impactful learning experiences, our knowledge development processes will be guided by an equity and inclusion lens that not only promotes diversity but also eliminates barriers to learning. An inclusion, diversity, equity, and accessibility (IDEA) framework that demonstrates the intersection between education development and IDEA principles will be the cornerstone of this knowledge to practice initiatives. Developing education using this framework will ensure that instructional designers, subject matter experts, and faculty members reflect on and question their biases and assumptions throughout the education development, delivery, and evaluation cycle. Explicit reflections are critical for eliminating biases in dominant educational cultures that marginalize certain populations [30]. An equity lens in design is also foundational to building programs that are safe and accessible to diverse learner populations [31]. Within the context of the COVID-19 pandemic, our programs will be delivered through a web-based format. Unlike in-person learning, we recognize that web-based learning tends to be built on Eurocentric and ableist paradigms [30] and that web-based delivery may impede the equitable and accessible distribution of new knowledge. Therefore, leveraging the IDEA framework will afford the intentional integration of accessible and equitable practices into web-based delivery. To this end, the use of universal design learning for accessible and flexible learning is intended to build a web-based environment that is inclusive of all learners, harnesses the strengths of learner diversity, includes principles of culture and intersectionality, and creates a sense of belonging for all participants [30,32].

Phase 3: Assess Barriers and Facilitators

Overview

In the third phase, we aim to identify potential barriers and facilitators related to the adoption of AI in health care. As part of the needs assessment, a qualitative study will be conducted with former AI education participants and patient partners to understand the gaps and barriers with the current AI curriculum for health care providers. The findings will enable us to identify determinants of the evidence-practice gap, specific factors that influence the adoption and implementation of AI in clinical settings, and the specific targets to be addressed by our education interventions. This will generate a thorough understanding of health care providers' and patients' perceptions in enhancing and optimizing health care delivery through the use of AI. A survey will also be disseminated to health care providers across Canada to better understand learners' needs when developing the curriculum.

Needs Assessment: Study Population and Sampling

Key informants will comprise health care providers (any practice setting), leaders, and scientists who have taken part in an AI education program, as well as patient partners. Health system leaders are those enabling and empowering other professionals to integrate AI into the health care setting. We anticipated needing 30 to 40 interviews with key informants given the variety of perspectives, different health professions, and geographic location [33].

Needs Assessment: Recruitment Procedure

Qualitative Interviews: Existing AI Programs Offered Through Michener Institute of Education at University Health Network and Vector Institute

The Michener Institute of Education at University Health Network (UHN) and the Vector Institute offer several AI programs for equipping learners with AI skills and competencies sought by the industry. This includes the AI Certificate program and the Special Topics course at the Michener Institute of Education at UHN [34], as well as the AI programs accredited by the Vector Institute, such as the University of Toronto's Master of Health Informatics program. A purposive sampling approach will be used to ensure that there is diversity in the types of health professionals and executives, age, years in practice, locations of practice (urban vs rural), and types of health organization (academic, community, and independent practice). We will reach out to the Michener Institute of Education at UHN and the Vector Institute leads, part of this project team, for a list of participants who have taken part in an AI program that was targeted for health care providers and leaders at their institutions.

Qualitative Interviews: Environmental Scan and Scoping Review

AI programs will be identified through an environmental scan and scoping review, the purpose of which is to understand the

current landscape of AI education programs and gain important insights into successful education development. The program leads for courses that are publicly listed on their websites will be contacted and asked to send email invitations to their educators and learners on behalf of the project team. Three to five participants will be interviewed at each organization.

Qualitative Interviews: Project Partners and Snowball Sampling

In addition, participants will be recruited via partner organizations for this project. This will include email invitations sent on behalf of the research team by the education committee members of those organizations. Those who have consented to be part of the study will be asked to inform colleagues within their networks and share the research analyst's contact information with those interested in participating.

Qualitative Interviews: Patient Partners

Patient partners will also be purposively sampled through partner organizations. Discussions with patient partners will help us to understand where there are gaps in AI education for care providers and where they would like them to be knowledgeable about using AI. It is imperative to consider patient partner input when creating content relating to patient interactions and considerations.

Survey: Partner Organizations

The survey will be disseminated through our partner organizations. We will also reach out to our community of interest that we are building for this project, such as through the events hosted and the sign-up list. When registering for the event, they have the option to receive news about upcoming initiatives, tools, and learning opportunities. There is also a sign-up list on the Michener Institute of Education at UHN website for individuals to sign-up to receive electronic communications about the project.

Needs Assessment: Data Collection

Qualitative Interviews

We will conduct semistructured interviews with key informants; this methodology will allow for further exploration of any issues participants may reveal as significant. An interview guide will be used to review participant experiences and suggestions for developing AI curricula, which will include questions on motivations for AI education program registration, the relevance of subject material to participants, and barriers to engagement with further AI-related education initiatives. This guide will be revised iteratively with each interview, as necessary. Each interview will be conducted and, recorded through Microsoft 365 Teams app and transcribed using NVivo 12 (QSR International). Interview length may vary based on the participant's level of comfort in sharing their experiences.

Survey

A survey will be disseminated to health care professionals across Canada to better understand their perceptions and adoption of AI in clinical practice.

Needs Assessment: Data Analysis

Qualitative Interviews

Transcripts will be analyzed thematically using an iterative, inductive, and constant comparative process. The flexibility of the thematic analysis allows the researcher to report the experiences, beliefs, and reality of participants in rich detail [35]. Most importantly, it establishes a more systematic and explicit form of examining data without losing the rigor of the analysis [35]. Two study reviewers will analyze the transcripts independently from the first three interviews to identify codes and shape further data collection. The team will collaboratively develop an initial coding structure. Data will be inductively analyzed following the systematic process outlined by Braun and Clarke [35]. New data will be constantly compared with existing data, resulting in an iterative refinement of the coding structure. Any discrepancies in coding will be discussed with the team until a consensus is reached. QSR NVivo 12, a qualitative data analysis software program, will be used to examine responses to emerging and recurring themes. Data collection and analysis will continue until theoretical saturation is reached. To ensure transparency and rigor, we will collect field notes, and an audit trail of each team member's independent coding, team meeting notes, and different versions of the coding structure will be maintained. In addition, the quality of the thematic analysis will be assessed using Braun and Clarke's [36] twenty-question evaluation tool.

Survey

Descriptive statistics will be used to analyze the close-ended quantitative survey data. Software program GNU Affero General Public License R Studio and IBM SPSS will be used to report the descriptive statistics. Content analysis will be used to analyze open-ended qualitative survey data in two distinct phases: deductive and inductive.

Phase 4: Launch Intervention

Overview

In phase 4, our aim will be to develop knowledge translation products that promote awareness and the use of knowledge to harness data and AI to enhance care delivery. In a recent Harvard Business Review article, Fountaine et al [37] argued that culture, rather than technology, is a major challenge in adopting AI. The authors provided guidelines on establishing internal structures and proposed a flexible hub and spoke model, which will help organizations scale. This model focuses on expertise that is both centralized to ensure consistency in strategies, procedures, and partnerships and decentralized to ensure that the work is ingrained in essential business activities and performance improvement [28,37]. This fluid model is vague in terms of responsibility. Depending on an organization's structures, capabilities, strategies, and unique characteristics, work can be transitioned between centralized and decentralized responsibilities [6,28]. This study further highlights the need to educate everyone. The type of education required is based on an individual's role; this can be a formidable task within the context of the exponential growth of digital technologies and the growing divide between the emergence of technologies and organizational readiness [28,37]. Most health care providers

have not been educated on the effective, appropriate, safe, and compassionate use of AI, yet they must safely adopt these tools and shift their scope of practice. The process of implementing AI-enabled technologies in health care organizations must be prudently considered as care providers have the obligation to do no harm [28]. Health care providers should have the necessary knowledge to shape the future of AI-enabled care.

Using the data obtained from phases 1 to 3, we will develop four knowledge translation interventions that will accelerate the rate of organizational change and ensure that AI enhances and optimizes health care delivery (Figure 3). The interventions include engagement activities to increase AI awareness (intervention A), a certificate-based intervention to educate health care providers about AI (intervention B), a certificate-based intervention to educate health system leaders about AI (intervention C), and a coaching and practice-based innovation hub (intervention D). The interventions will help increase health care providers' and leaders' knowledge, confidence, and skills in integrating AI as part of their practice.

The program design and delivery in the pilot phase will be based on empirical evidence and expert consensus of curricula content, specifically, what is feasible in our specific context. The proposed program will be designed to transform the mindsets, skillsets, and toolsets of health care providers, thereby accelerating the appropriate adoption of AI. The curricula will be developed with an instructional designer through an iterative process that follows the successive approximation model [38]. Subject matter experts and other stakeholders will be engaged during the design and development process to provide feedback and continuously improve curricula. Before the release of the final version of the educational interventions, usability testing will be conducted to ensure that end-user perceptions, requirements, and information needs are met. Usability testing is crucial for identifying errors, participant decision-making, and reasoning skills, as they perform specific tasks. Usability testing will be guided by Nielsen's 10 Usability Heuristic Principles and Severity Scale. The heuristic analysis will serve as an evaluation method to examine the user interface and to identify issues so that they can be resolved, thereby improving user satisfaction and experience. The findings will be used to further tailor and iteratively refine the program (see Table 2 for the prospective design of the education interventions).

Figure 3. Knowledge translation interventions. AI: artificial intelligence; IDEA: inclusion, diversity, equity, and accessibility framework.

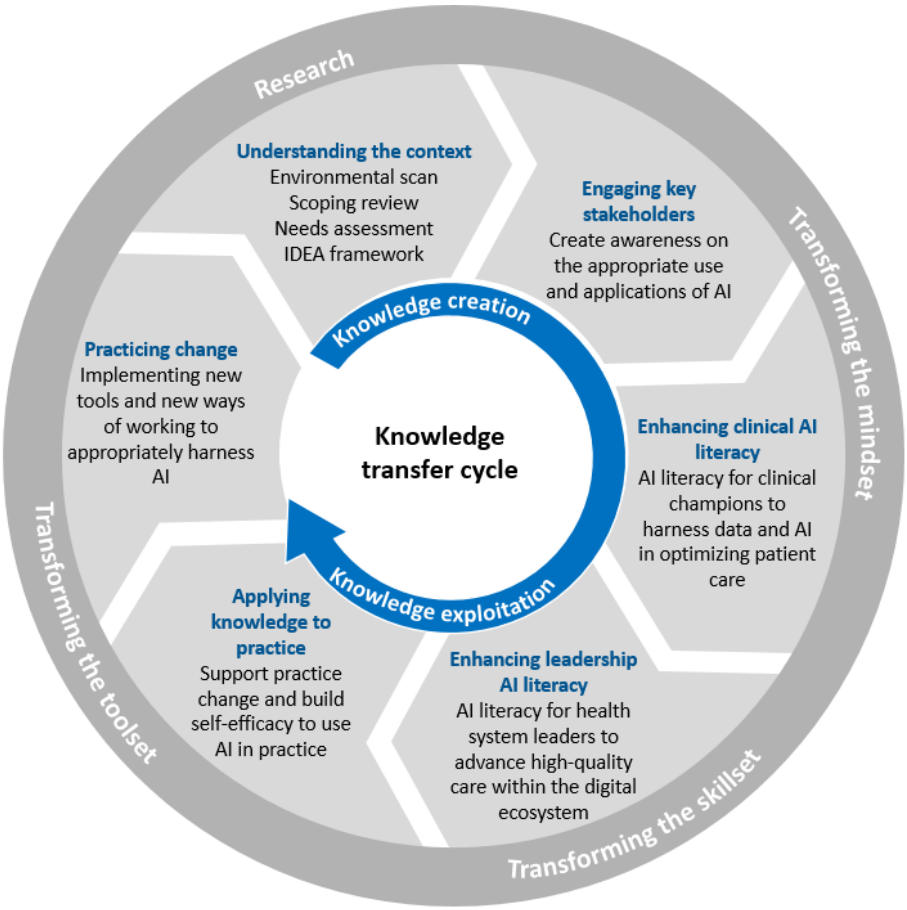


Table 2. Prospective design of education interventions.

Education intervention	Target audience (sample size)	Prospective format
A: Engagement activities to increase awareness	5000 participants	• Synchronous and asynchronous
B: Certificate-based intervention to educate health care providers about AI[a]	25-50 health care providers	• Synchronous and asynchronous • 4-6 modules • Closed registration
C: Certificate-based intervention to educate health system leaders about AI	25-50 health system leaders	• Synchronous and asynchronous • 4-6 modules • Closed registration
D: Coaching and practice-based innovation hub	20 teams within AI projects	• Community of practice • Goal setting and reflection-based activity • Closed registration

[a]AI: artificial intelligence.

Education Interventions A-C

The interventions will be designed and iteratively adapted based on learners' needs identified through knowledge creation activities. These interventions are anticipated to incorporate both synchronous and asynchronous elements so that learners can prepare for, and engage in, interactively. Instructional strategies include reflection exercises, participant-led discussions, and sharing of course materials. Prospective curriculum topics include AI fundamentals, AI in health care, ethics, data science, and the challenges to and opportunities for using AI.

Education Intervention D

The coaching and practice-based hub will support health care providers in implementing high-impact projects, thus building momentum for AI-enabled care. The hub leverages the structure of our in-house personalized learning program [39], which is a fully personalized and engaging observership-based program intended to meet learner goals [39]. The personalized learning program structure ensures that no two programs are the same, as each project or learner presents unique needs. By leveraging this structure, we will also use various resources and expertise throughout the country to align with the learners' professional development goals. Coaching and mentoring time and education opportunities, such as workshops will be scheduled within the education plan as applicable. This opportunity will provide learners with an immersive experience, in an environment with expertise in both AI adoption and implementation, and teams that will support the learners by linking their learning to their own institution and projects. Learners will be matched with an expert coach. With this experience, we hope to give learners the confidence to take great ideas and adapt them to fit into their environments. This experience will also be an opportunity to network with AI leaders across the country.

There is an imperative need to mobilize knowledge across professions and organizations to address the gap between technological change and organizational readiness. Web-based learning can expand the reach of our project's coaching and practice-based intervention, which may enable a more diverse cross-section of projects that can be coached. This expanded reach will enable an interprofessional community of practice (CoP), developed initially by Wenger et al [40]. CoP provides an ideal setting to identify knowledge and skill gaps to pursue learning with colleagues and experts to fill these gaps. Li et al [41] highlighted several key characteristics to guide the development of a community practice, which include formal and informal interaction between the learners and the experts, importance on learning and sharing knowledge, and nurturing a sense of acceptance among members of the community. The authors further asserted that a learning community provides a safe environment for individuals to engage in learning through collaborative discussions with other members and experts in the field [41]. This research will contribute to our understanding of the role and impact of CoPs in translating AI knowledge into practice.

Phases 5 and 6: Pilot Evaluation

Overview

In phases 5 and 6, a pilot evaluation will be conducted to evaluate each educational intervention and to determine if the desired outcomes are achieved. A multimethod evaluation approach will be guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [42]. The RE-AIM framework will enable us to assess whether the interventions are effective in enabling care providers to harness AI in optimizing health care delivery, and the curricula are reflective of best practices. The survey questions will be guided by the RE-AIM framework to measure the reach, effectiveness, adoption, implementation, and maintenance of educational interventions [42]. Interventions will be iteratively updated and refined using a developmental evaluation strategy. Interventions A to D will be observational pre- and posttest methods, including mixed methods design consisting of surveys and interviews to understand and assess the impact of the intervention from a quality improvement perspective. In addition, intervention D will consist of goal setting and reflection exercises (Table 3 lists the research methods).

Table 3. Multimethods for evaluating education interventions.

Aim and data collection format	Education intervention
Understand why certain curriculum topics are important and the level of receptivity toward and engagement in implementation of AI[a] in their practice setting	
• Surveys • Interviews or focus groups	A: engagement activities to increase AI awareness
Explore their perceptions of the program, whether it influenced them to seek out further learning, identify curriculum topics of interest, topics to prioritize, and their professional background	
• Pre- and postsurvey • Interviews or focus groups	B: health care providers
• Pre- and postsurvey • Interviews or focus groups	C: health system leaders
• Pre- and postsurvey • Reflections • Interviews or focus groups	D: coaching and practice-based innovation hub

[a]AI: artificial intelligence.

Study Population and Sampling

For education interventions A to D, participants will include any individuals 18 years or older who have registered for the intervention and have shared their names, full mailing addresses, and email addresses. Engagement activities are intended to create awareness and increase the ability of health care providers to engage in AI-based initiatives. In addition, there will be two certificate-based interventions developed specifically for health care providers and leaders. Registration is open to health care professionals with a particular focus on those working in the health system. Health care professionals are defined as staff who provide health care services to patients and include clinical, administrative, and other nonclinical staff. Health system leaders are considered champions who will be actively involved in essential conversations at all levels of the organization and help put AI into practice. For the coaching and practice-based intervention, participants would include health care providers and leaders working in the National Health Care System and those who have an interest or identify the need to advance their data literacy and AI knowledge. Eligibility criteria also include the ability to have advanced proficiency in reading, writing, and speaking English, because all components of these activities are available only in English. The response rate is not anticipated to be affected by this English proficiency criterion. Engagement materials with participants will be offered in English and French; however, the evaluation components will only be in English.

Recruitment Procedure

Prospective program participants (for interventions B-D), including health care providers and health system leaders, will be recruited using various channels, such as national specialty societies across health professions and leadership associations [43-44]. Participants can also self-identify through earlier project activities, such as needs assessment. For the coaching and practice-based innovation hub (intervention D), participants in the coaching will also be recruited from AI certificate interventions developed by us, and via the Michener Institute of Education's and the Vector Institute's social media platforms. Potential candidates will be selected through an interview process and matched with a coach on the basis of learning objectives and area or areas of expertise. Coaches for intervention D will be recruited from a pool of experts and leaders in AI faculty from the certificate programs we developed as well as through provincial AI incubators and think tanks. Coaches are required to provide their expert profiles to facilitate the matching process.

Data Collection

Pre- and Postsurvey

The quantitative phase consisted of a pre- and postsurvey for each education intervention evaluation. The presurvey consists of three sections: (1) demographics and practice context, (2) engagement in AI-related education, and (3) motivation level for learning. The motivation level for learning will be measured using the Jefferson Scale of Physician Lifelong Learning (JeffSPLL), which consists of 14 items, and generates scores ranging from 14 to 56. Higher scores denote greater affinity for lifelong learning [45]. The JeffSPLL consists of three factors: learning beliefs and motivation, attention to learning opportunities, and information-seeking technical skills. The reliability of the JeffSPLL scale is 0.77 to 0.86 in the previous studies [45].

The post survey consists of two sections: (1) experiences with the program and (2) usability of the educational activities offered on the web. The surveys were structured based on the Moore framework [46]. Questions are both quantitative and qualitative (ie, open responses) in nature. The majority of the survey is quantitative, requiring participants to select from a radio list of options, or a 5-point Likert scale ranging from *strongly disagree* to *strongly agree*. For instance, in section 1 (thoughts about the program), participants will answer the following questions using a 5-point Likert scale for each program: (1) "My knowledge and awareness of this topic increased;" (2) "The topics covered in this program are relevant to me." Examples of qualitative or open-ended questions for section 1 include, "which topics were

missing or you wish were covered in more depth and why?" In section 3, the System Usability Scale (SUS) is used to measure the usability of educational activities offered on the web [47]. The SUS is a 10-item questionnaire with five response options and generates a score ranging from 0 to 100. The average SUS score was 68; thus, higher scores indicated better usability.

Qualitative Interviews or Focus Groups and Reflection Exercises

The qualitative phase will consist of two data collection methods: semistructured interviews or focus groups for each education intervention evaluation. Semistructured interviews and web-based focus groups were chosen as the optimal methods because they provide the opportunity to capture richer descriptive data around participants' behaviors, motivations, and experiences [48]. In addition, focus groups are an opportunity to allow participants to understand and hear differences of opinion and build on each other's statements [49].

For interviews and focus groups, maximum variation and purposive sampling [50] will be used to explore the phenomena of interest across a range of demographically varied participants. Approximately, 15-20 participants from within the education program cohort will be selected to participate in a semistructured interview or focus group [33]. Questions will explore phase 1 findings to (1) understand the knowledge gain and applications of knowledge structured by the Moore framework [46]; (2) elicit feedback on the program curriculum, delivery, and format; and (3) understand contextual factors structured by the Nonadoption, Abandonment, and Challenges to Scale-up, Spread, and Sustainability framework [51]. The Moore framework will provide a structure to explore education outcomes at the individual, organizational, community, and system levels, with a particular focus on assessing the impact on patient care [46]. From a technological perspective, the Nonadoption, Abandonment, and Challenges to Scale-up, Spread, and Sustainability framework [51] will allow us to explore contextual factors that will affect the success of the program and the adoption of AI and related emerging technologies, including organizational culture, technological factors, individual attitudes, and organizational factors, including readiness for change and systems issues. Interview data will be deductively analyzed using the constructs from these frameworks as predefined codes. The interview guide will be iteratively enhanced during each interview conducted. Each interview will be audiotaped, and professionally transcribed.

Furthermore, for coaching and practice-based intervention, a goal assessment document will be used to set expectations and learning objectives. Reflection experience documents will be submitted by mentees at the 3- and 6-month marks. These documents will assist mentees in reflecting on their experiences and identifying areas of personal, professional, and academic growth**.** The reflective approach is guided by the Kolb experiential learning theory. Kolb asserted that learning is a process in which knowledge is generated through experiences [52]. Specifically, immediate personal experience enables one to observe and reflect, which can be assimilated into abstract concepts, guiding learners to create new experiences [52]. Thus, the coaching and practice-based innovation hub built on the four stages of experiential learning theory would elicit evidence for changes in cognitive processes, learning, and behavior.

Data Analysis

Pre- and Postsurvey

Descriptive and content analyses will be used to determine: (1) who participated in this program; (2) if participants increased their knowledge of the scope of AI, automation, and machine learning in the Canadian context; (3) if participants received the information they were hoping for, and if not, what was missing; (4) of the information received, what was critical or most relevant; (5) if participating in this program prompted participants to seek further learning; and (6) if the participants planned to seek or participate in further learning. Descriptive statistics will be used to analyze the closed-ended survey questions, and an iterative, inductive method of constant comparative analysis will be used to analyze the open-ended responses [53]. Content analysis enables a systematic and objective means of describing the characteristics of a phenomenon [54,55]. Interview and focus group data will be analyzed using an open coding process consisting of meaningful words and phrases.

Qualitative Interviews or Focus Groups and Reflection Exercises

Audio recordings of interviews and focus groups will be transcribed, and open-ended responses to goal assessment and reflection experience documents will be collected. Data will be first analyzed deductively using the Moore framework [46]; predefined codes generated on the basis of the different outcomes of the Moore framework will then be inductively analyzed, followed by a systematic process outlined by Braun and Clarke [35]. Two study reviewers will independently analyze the transcripts from the first three interviews or focus groups to identify codes, and the team will collaboratively develop an initial coding structure. The coding structure will be iteratively refined by constantly comparing new data with existing data. Data collection and analysis will continue until theoretical saturation is reached. Any discrepancies in coding will be discussed with the team until a consensus is reached. Triangulation will be used to establish the themes. QSR NVivo 12 will be used to examine the responses to emerging and recurring themes.

Phase 7: Sustain Ongoing Knowledge Use

Strategies to sustain ongoing knowledge use were considered in this project, including ensuring participation from important stakeholders and an evaluation to gain useful insights on emerging learning needs and support the optimization of educational interventions. As part of the coaching and practice-based innovation hub, an interprofessional CoP will have been established to share experiences and allow for the creation of new knowledge to advance the field of AI in health care. Hence, it is imperative to consider strategies on how the CoP will be sustained with former participants and engage prospective learners to build a dynamic web-based learning community. The findings will be used to inform appropriate dissemination strategies and the sustainability of the program.

Governance

The governance model has an overarching goal of establishing and sustaining the alignment of strategic priorities to enhance transparency and communication pathways, and ultimately support the achievement of the deliverables set out in the Future Skills Grant project. The governance structure will follow a four-tiered model, in which day-to-day operations and activities related to individual projects will be discussed at the task force for decision-making and identification of issues requiring escalation. The task force will seek advice from the Scientific Advisory Council and the Program Development Advisory Council. Demand, ongoing initiatives, and escalations will be shared at the steering committee level for informational purposes, resolution, decision-making, and analysis of cross-project impact. Key items will be presented at the executive level, primarily to seek guidance in decision-making and to provide any ongoing updates. To put the needs of patients first in creating a healthier world using AI, we will involve patient partners in the design and development of our education programs. They will be engaged in defining the success of the programs and ensuring that they are meaningful to the target population.

Results

This study is currently under review by the institutional review board of the UHN. Due to the large, complex nature of this initiative, the research ethics board requested that the submission be completed in phases. Informed, implied consent will be obtained based on the completion of the survey, and informed written consent will be obtained before proceeding with the semistructured interviews or focus groups. We will conduct preliminary data collection for educational interventions in 2021. These results are expected to be published in 2022.

Discussion

Short-term and Medium-term Outcomes

This proposed study will be designed to transform the mindsets, skillsets, and toolsets of health care providers across Canada, accelerating the appropriate adoption of AI. Preliminary results indicate that there is a need for national education standards, competency-based frameworks, and evaluation approaches. Participants will have increased knowledge of AI to have necessary and essential conversations at all levels of the organization. In addition, a framework on the capabilities and competencies of future AI workforce will be developed based on the findings from the needs assessment, including the environmental scan and scoping review. This study will develop knowledge translation interventions for the adoption and implementation of AI tools in clinical practice.

Long-term Outcomes

In the long term, health care providers will have developed the required competencies and capabilities to adapt their practices in an AI-enabled environment. This project will create a culture of trust and transparency with stakeholders by establishing awareness and building the capacity and capability to have meaningful conversations about AI and its applicability. The interventions we developed assist organizations in educating health care providers and leaders to have access to knowledge products for the adoption and implementation of AI tools. The education program is designed to support organizations to more rapidly adopt AI technologies with confidence, knowing that health care providers have the appropriate knowledge and skills.

Dissemination

Research activities are designed to engage key stakeholders, solicit feedback about the project, and disseminate findings. As part of the integrated knowledge translation and community-building efforts, the project team will be posting on social media and creating engagement activities such as AI blog posts, infographics, and video vignettes to establish awareness and engage potential participants in upcoming education programs. Stakeholders will be engaged and briefed at every stage of the KTA framework. The feedback will be used to further refine the programs to meet the learners' needs. Dissemination is a part of a dynamic and iterative process that entails building relationships among key stakeholders. The final results will be disseminated via nontechnical briefs, round table discussions, symposia, conference presentations, and publications.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CoP: community of practice
EHR: electronic health record
HIS: health information system
IDEA: inclusion, diversity, equity, and accessibility
JeffSPLL: Jefferson Scale of Physician Lifelong Learning
KTA: Knowledge-to-Action
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SUS: System Usability Scale
UHN: University Health Network

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Protocol

Remote Blood Pressure Monitoring With a Wearable Photoplethysmographic Device (Senbiosys): Protocol for a Single-Center Prospective Clinical Trial

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Abstract

Background: Wearable devices can provide user-friendly, accurate, and continuous blood pressure (BP) monitoring to assess patients' vital signs and achieve remote patient management. Remote BP monitoring can substantially improve BP control. The newest cuffless BP monitoring devices have emerged in patient care using photoplethysmography.

Objective: The Senbiosys trial aims to compare BP measurements of a new device capturing a photoplethysmography signal on the finger versus invasive measurements performed in patients with an arterial catheter in the intensive care unit (ICU) or referred for a coronarography at the Hospital of Fribourg.

Methods: The Senbiosys study is a single-center, single-arm, prospective trial. The study population consists of adult patients undergoing coronarography or patients in the ICU with an arterial catheter in place. This study will enroll 35 adult patients, including 25 patients addressed for a coronarography and 10 patients in the ICU. The primary outcome is the assessment of mean bias (95% CI) for systolic BP, diastolic BP, and mean BP between noninvasive and invasive BP measurements. Secondary outcomes include a reliability index (Qualification Index) for BP epochs and count of qualified epochs.

Results: Patient recruitment started in June 2021. Results are expected to be published by December 2021.

Conclusions: The findings of the Senbiosys trial are expected to improve remote BP monitoring. The diagnosis and treatment of hypertension should benefit from these advancements.

Trial Registration: ClinicalTrials.gov NCT04379986; https://clinicaltrials.gov/ct2/show/NCT04379986

International Registered Report Identifier (IRRID): PRR1-10.2196/30051

(JMIR Res Protoc 2021;10(10):e30051) doi:10.2196/30051

KEYWORDS

continuous blood pressure monitoring; photoplethysmography; arterial line; Senbiosys; wearable devices; blood pressure; remote monitoring; continuous monitoring; mHealth; mobile health

Introduction

Systemic arterial hypertension is a major modifiable cardiovascular risk factor [1]. The 10-year incidence of hypertension in the Swiss population has been estimated to be almost one-third [2]. Many patients with hypertension are aware of their condition but are either untreated or inadequately treated, although effective treatment of hypertension reduces morbidity and mortality rates [3].

Remote blood pressure (BP) monitoring—accompanied by education on hypertension management by caregivers—can substantially improve BP control. Wearable devices can provide user-friendly, accurate, and continuous BP monitoring to assess

patient's vital signs and achieve remote patient management [4-6].

The newest cuffless BP monitoring devices use photoplethysmography (PPG) [6,7]. This method consists of emitting light to the skin through a light-emitting diode and then measuring the changes in light absorption to a photodiode to detect peripheral volumetric variations of blood circulation [8]. A PPG waveform has been proven to correlate well with BP waveforms and truly represents one cardiac cycle, comprising the systolic peak, the diastolic peak, and the dicrotic notch [9,10]. One of the main challenges of this technique is to obtain an accurate estimate from the different PPG morphologies that are affected by patient's characteristics, including age, vessel stiffness, cardiovascular disease, and other hemodynamic properties [11,12].

The Senbiosys device uses a PPG-based pulse wave analysis technique, which involves morphological analysis of the PPG pulse waveform thanks to an algorithm that identifies combinations of features of the PPG waveform to estimate BP [13,14]. Moreover, the PPG signal quality strongly depends on the body location [15]. In this regard, the Senbiosys PPG technology captures the PPG signal in the finger, which is known to be one of the best locations in terms of signal fidelity. The accuracy of the PPG-based technology is of fundamental importance, and several validation procedures for assessing the precision of BP monitoring devices have been developed [16].

The purpose of this study is to evaluate the accuracy of the Senbiosys device for measuring BP compared to invasive BP measurements with the arterial line, the gold standard in the hospital setting. Participants will undergo invasive BP estimation and will simultaneously wear the Senbiosys device.

Methods

Study Setting

This is a single-center, single-arm, prospective trial aiming to assess the accuracy of the Senbiosys device to estimate BP versus the invasive BP measurement. The patients will undergo invasive BP estimation and will simultaneously wear the device. This study will enroll 25 adult patients addressed for a coronarography and 10 patients in the intensive care unit (ICU). The intervention period that the devices are worn is between 10 and 15 minutes for each patient. There is no follow-up period after intervention.

Inclusion and Exclusion Criteria

All patients 18 years or older either referred for coronarography or in the ICU requiring invasive BP monitoring and with an arterial catheter in place are eligible for the study. A modified Allen test will be routinely performed prior to arterial catheterization as per clinical routine.

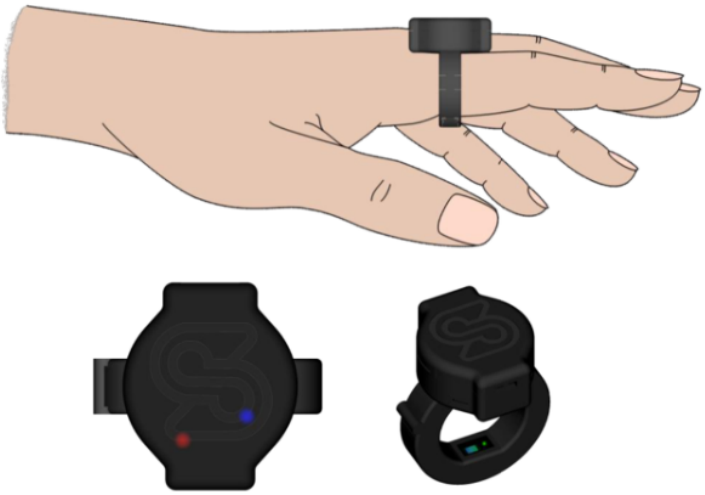
The presence of any of the following exclusion criteria will lead to exclusion of the participants:

- Patient unable or unwilling to provide written informed consent themselves, which presupposes the patient's capacity for discernment
- Coronarography in patients with myocardial infarction
- Patient with suspected or certified COVID-19 infection
- Patients with atrial fibrillation
- Patients with intracardiac monitoring
- Significant noninvasive systolic BP (SBP) difference between left arm and right arm (difference >20mmHg in systolic arterial pressure)

Intervention

The investigated device is the SBF2003, manufactured by Senbiosys, which is a ring measuring the patient's PPG on the fingers. The intervention period that the devices are worn is between 10 and 15 minutes for each patient. The way the device is worn on a finger is depicted in Figure 1.

Figure 1. SBF2003 and the way the device is worn on a finger during operation.



Standardized Measures in the Cardiac Catheterization Laboratory

The investigator will put the ring on the index finger of the patient's hand. The device will be placed prior to the placement of the sterile field and will not be in contact with it. Arterial puncture will be performed either via the radial or femoral access according to the clinician's choice. Intra-arterial BP waveforms will be recorded using a fluid-filled catheter. The catheter will be flushed before any waveform recordings are made. At first, the catheter will be positioned in the aorta for 3 minutes of stable BP waveforms recording. Intracoronary nitroglycerin will be administered at a dose of 300 µg. At the end of the coronary angiography, an additional 3 minutes of recording will be performed in the aorta.

Standardized Measures in the Intensive Care Unit

The investigator will put the ring on the same arm of the arterial catheter for simultaneous measurements. Enrolled patients must have had an arterial catheter in place at the time of inclusion to the study. No arterial catheters were placed for the sole purpose of this study. Arterial catheterization will be performed by the intensive care team according to current medical guidelines.

Outcomes

The primary outcome is the assessment of mean bias (95% CI or precision of bias) for SBP, diastolic BP (DBP), and mean BP (MBP) between invasive and noninvasive BP measurements. The standard deviation of the bias (95% limits of agreement) will be assessed for SBP, DBP, and MBP measurements.

The percentage of signal with artifact, therefore not useable, will be determined. In this regard, secondary outcomes include a reliability index (Qualification Index) for BP epochs and count of qualified epochs.

Participant Timeline

The timeline for enrollment, intervention, and data collection is outlined in Table 1.

Table 1. Timetable of patient enrollment and intervention and data collection.

Study schedule	Patient information and inclusion	Intervention period
Visit 1	0	1
Time	≥12h before procedure	0
Patient information	✓[a]	—[b]
Informed consent	✓	—
Baseline characteristics: age, gender, CVRF[c], etc	✓	—
BP[d] recordings	—	✓
Primary outcome	—	✓
Secondary outcome	—	✓
Safety outcome	—	✓

[a]This item is included.

[b]This item is not included.

[c]CVRF: cardiovascular risk factor.

[d]BP: blood pressure.

Sample Size

The sample size is chosen based on the recommendations of the ISO 81060 guidelines [17] to determine the feasibility of noninvasive BP monitoring. Based on previous research, study sample size calculations for validation of BP measuring devices showed that 35 individuals is adequate for a high accuracy device (defined as mean BP difference between reference and test device measurement 0, SD 3-6 mmHg) [16]. Consensus was reached that studies performed on the general population should include adult participants; both individuals who are hypertensive and normotensive; ≥30% males and ≥30% females; ≥5% of the reference systolic BP readings ≤100 mmHg, ≥5% with ≥160 mmHg, and ≥20% with ≥140 mmHg; and ≥5% of reference diastolic BP readings ≤60 mmHg, ≥5% with ≥100 mmHg, and ≥20% with ≥85 mmHg. Due to the heterogenicity of patients to be included, we plan to enroll 25 patients in the cardiac catheterization laboratory and 10 patients in the ICU.

Recruitment

Eligible participants will be identified via the principal investigator throughout the study period. The presence of exclusion criteria will be defined according to the patient's clinician in charge. Patients' capacity for discernment will be functionally assessed by the clinician in charge to determine whether the patient is capable of making a specific decision and whether the patient is capable of giving informed consent. If the eligibility criteria are met the patient will be formally enrolled. The written informed consent form will be signed by the patient and by one of the principal investigators. Only patients with the ability to provide consent in the ICU and the coronary care unit will be included.

Based on the current statistics for admissions to the ICU and cardiac catheterization laboratory in our institution, we estimate a total duration of 4 weeks for patient enrollment and the assessment of the primary and secondary end points.

Data Collection

Patient characteristics and study outcomes will be transferred into an electronic case report form (REDcap Software, Vanderbilt University) designed to capture study information on the informatic structure of the HFR Fribourg. During the clinical trial, data will be accurately recorded, and the original documents will be stored at the clinical trials unit of the University and Hospital of Fribourg, under locked conditions when not in use.

Statistical Methods

Categorical variables will be reported as counts and percentages; continuous variables will be reported as mean and SD or as median with 25% to 75% IQR according to their distribution as root mean square error. Normality will be assessed by visual inspection of histograms, the computation of Q-Q plots, and the Shapiro-Wilk test. Categorical variables will be compared using chi-square or Fisher exact test as appropriate. Continuous variables will be analyzed using the Student *t* test or the Wilcoxon rank sum test according to their distribution. Categorical variables fall into 3 groups representing the limit of the absolute BP differences: ≤5 mmHg, ≤10 mmHg, and ≤15 mmHg. Both arterial line and Senbiosys device signals will be segmented to epochs of duration (10-45 seconds). BP values will be computed for each epoch. Furthermore, for each epoch, we will compute the reliability index. Epochs with reliability indexes above a given threshold will be qualified for our study. Bland-Altman plots for repeated measures will be used to analyze SBP, DBP, and MBP data collected from the Senbiosys device and the arterial line [18]. Mean difference in scores (bias) and 95% limits of agreement, including the differences between noninvasive and invasive measurements (bias ± 1.96*SD), will be computed. Pearson correlation will be used to characterize the relation between noninvasive and invasive BP measurements. The acceptable bias and precision for arterial pressure measurements were fixed a priori at <5 and 8 mm Hg, respectively [16]. All statistical analyses will be performed using Matlab R2019a (MathWorks).

The null hypothesis is that the difference between invasive and noninvasive methods of BP calculated by Bland-Altman analysis are not within the clinically acceptable range.

Analysis

All statistical analyses will be performed using Matlab R2019a. Blinded data analysis will be performed.

Monitoring

The monitor is an independent trial monitor that will perform all the on-site monitoring activities. The monitor is qualified in the field of the International Standard through training and experience as well as scientific or clinical knowledge. The monitor will ensure that the clinical site understands and follows the protocol; he will review the completeness and accuracy of source data and study documents. Monitoring visits will be performed at the beginning, middle, and end of the study. Source data and documents are accessible to the monitor, and questions are answered during monitoring visits.

Harms

Since the Senbiosys measurements will not be interpreted in the clinical context, there is no risk of misdiagnoses. Adverse device effect includes the risk of developing a cutaneous allergic reaction. However, this risk is minimal given that the equipment used is of the medical type. In that case, the sensor will be removed earlier, and the patient excluded from the trial. There are no foreseeable interactions with simultaneous medical interventions, as the medical device is on the index finger and does not interfere with other actions. The risk analysis and risk assessment are performed according to EN ISO 1497.

Ethics and Dissemination

Research Ethics Approval

This study is conducted in compliance with the current version of the Declaration of Helsinki. The research project was approved by the local ethics committee of canton Vaud, Switzerland (CER-VD 2020-00996).

Protocol Amendments

The principal investigator is responsible for communicating important protocol modifications to the ethics committee and to the competent authorities, including the clinical trial registry (ClinicalTrials.gov NCT04379986).

Consent

The study nurse will collect patient information and provide a consent form with details on trial rationale, interventions, and potential benefits and harms. The patients will be given up to 24 hours to consider participation. Patients can withdraw their consent unconditionally, at any time, and without any justification. Medical data that have been collected to date will, however, be analyzed.

Confidentiality

The investigators will comply with local privacy laws. Anonymity of the participants will be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Participants' medical information obtained in this study is considered confidential, and disclosure to third parties is prohibited.

Access to Data

Data will be stored physically and electronically on a secure central server at the clinical trials unit at the University and Hospital of Fribourg. Physical data are protected by restricted access to their location. Electronic data are protected by the IT-Services of the state of Fribourg (SITEL services). The investigators will have access to the protocol, data set, and statistical code during and after the study for publication and dissemination. The study nurse will only have access to the data set during the study period.

Funding

The trial is supported by an unrestricted grant from the Fonds Scientifique Cardiovasculaire Fribourg.

Dissemination Policy

The study results will be disseminated within the department of cardiology and the ICU, and are intended to be published in peer-reviewed medical journals and communicated at medical conferences.

Results

This study was approved by the local ethics committee of the canton of Vaud, Switzerland (CER-VD 2020-00996) in March 2021. Patient recruitment started in June 2021. Data collection was completed by the end of June 2021. The results are expected to be published within 6 months of the end of the study.

Discussion

During the last couple of years, a growing number of wearable devices evolved to provide accurate, low-cost, and easily applicable monitoring of vitals parameters using PPG [19], A recent study by Pellaton et al [20] compared SBP and DBP values obtained by radial artery catheterization and those obtained from optical measurements (PPG) at the wrist. Unlike this study, we aim at focusing on the finger as a better location for PPG extraction and consequently BP monitoring. The results of Pellaton et al [20] were quite promising and justifies a further exploration on the finger by the means of SBF2003.

By demonstrating that the Senbiosys SA technology is reliable, we aim to substantially improve BP monitoring. This is particularly relevant both for prevention and ambulatory monitoring. The diagnosis and treatment of hypertension are expected to largely benefit from these advancements.

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Authors' Contributions

SS contributed to the study design and created the first draft of the manuscript. AC, AB, and SC conceived the original idea and planned the study. SS and AC contributed to the implementation of the research and data management. SS and AC contributed to the implementation of the research. SC supervised the project. All authors revised the manuscript critically for important intellectual content and consented to the publication. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
DBP: diastolic blood pressure
ICU: intensive care unit
MBP: mean blood pressure
PPG: photoplethysmography
SBP: systolic blood pressure

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Protocol

Delivering Cardiac Rehabilitation Exercise Virtually Using a Digital Health Platform (ECME-CR): Protocol for a Pilot Trial

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Abstract

Background: Exercise-based cardiac rehabilitation is recognized as a core component of cardiovascular disease management and has been shown to reduce all-cause and cardiovascular mortality and reduce the risk of hospital readmission following a cardiac event. However, despite this, the uptake of and long-term adherence to cardiac rehabilitation exercise is poor. Delivering cardiac rehabilitation exercise virtually (ie, allowing patients to participate from their own homes) may be an alternative approach that could enhance uptake and increase adherence.

Objective: The aim of this study is to assess the feasibility of delivering a virtual cardiac rehabilitation exercise program supported by the Eastern Corridor Medical Engineering – Cardiac Rehabilitation (ECME-CR) platform.

Methods: A convenience sample (n=20) of participants eligible to participate in community-based cardiac rehabilitation exercise will be recruited. Participants will be randomized to one of two study groups. Both study groups will perform the same exercise program, consisting of twice-weekly sessions of 60 minutes each, over an 8-week intervention period. Participants in the intervention group will partake in virtually delivered cardiac rehabilitation exercise classes in their own home. The virtual exercise classes will be delivered to participants using a videoconferencing platform. Participants in the control group will attend the research center for their cardiac rehabilitation exercise classes. Intervention group participants will receive the ECME-CR digital health platform for monitoring during the class and during the intervention period. Outcomes will be assessed at baseline and following the 8-week intervention period. The primary outcome will be exercise capacity as assessed using the 6-minute walk test. Other outcome measures will include heart rate, blood pressure, weight, percentage body fat, muscle strength, and self-reported quality of life. Semistructured interviews will also be conducted with a subset of participants to explore their experiences of using the digital platform.

Results: Participant recruitment and data collection will begin in July 2021, and it is anticipated that the study results will be available for dissemination in spring 2022.

Conclusions: This pilot trial will inform the design of a randomized controlled trial that will assess the clinical effectiveness of the ECME-CR digital health platform.

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KEYWORDS

cardiac rehabilitation; exercise; cardiovascular disease; virtual rehabilitation; digital health; self-management; pilot study; platform; feasibility

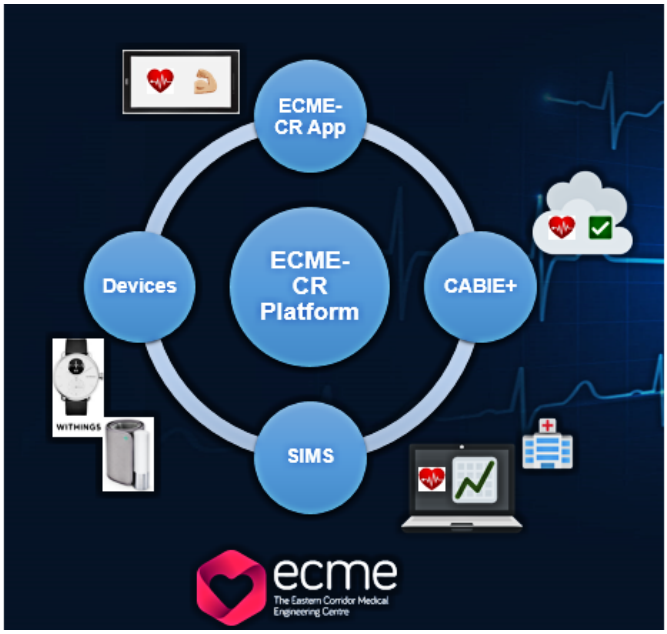
Introduction

Cardiovascular disease (CVD) remains the number one cause of death globally with age, high cholesterol, high blood pressure, smoking, and diabetes among the main risk factors. Although mortality from CVD has fallen over recent decades, it still results in 3.9 million deaths per year in Europe and costs the European economy €210 billion (US $248 billion) per year [1]. Due to improved survival rates, large numbers of people are living with chronic CVD. The effective management of those with CVD presents a significant challenge to health care systems globally.

Cardiac rehabilitation (CR) is recognized as a core component of CVD management, aiding in the recovery from an acute cardiac event and helping to prevent further illness and mortality. CR is generally prescribed to patients following a coronary angioplasty or coronary artery bypass graft, as well as to those with chronic heart failure. Cardiac rehabilitation typically includes nutritional counselling, risk factor management, psychosocial interventions, and lifestyle modification and education programs, as well as physical activity and exercise training. CR normally includes four phases of varying time frames: phase I (in-hospital patient period), phase II (postdischarge pre-exercise period), phase III (exercise and education program), and phase IV (maintenance). Phases III and IV are usually delivered in hospital outpatient departments or community centers. Active participation in the exercise training component of phases III and IV CR has been shown to be an effective tool in reducing all-cause and cardiovascular mortality [2,3], reduce the risk of hospital readmission [4], and have positive effects on cardiovascular risk factors, aerobic capacity, anxiety, and depression [4-6]. However, many patients do not receive appropriate CR. The COVID-19 pandemic severely impacted the delivery of CR services, with CR among the first clinical services to close at the onset of the pandemic [7]. However, even before the COVID-19 pandemic, CR was a significantly underused resource, with participation rates of around 40% being reported in recent years [8]. Multiple barriers to participation exist, such as distance to the CR center, lack of time, and the cost of rehabilitation [9]. As a result, calls have been made for alternatives to center-based rehabilitation programs [10]. Home-based CR has been advocated for many years and has been shown to be as effective as hospital-based CR in improving functional capacity [11]. The COVID-19 pandemic resulted in many CR services delivering classes virtually to patients via videoconferencing platforms [12]. However, with home-based and virtually delivered rehabilitation, clinicians have little insight as to how the patient is exercising and whether they are performing the exercises correctly and at a safe intensity. New innovative solutions are consequently required to support people with CVD to undertake their CR exercise safely and effectively at home.

In this paper, we present Eastern Corridor Medical Engineering – Cardiac Rehabilitation (ECME-CR), an interactive digital health platform (Figure 1) for cardiac rehabilitation developed by the Eastern Corridor Medical Engineering (ECME) research team at NetwellCASALA, Dundalk Institute of Technology. The platform has been designed to support the virtual delivery of CR exercise. The platform facilitates self-monitoring during the structured CR exercise class and during the intervention period.

Figure 1. Overview of the ECME-CR platform. ECME-CR: Eastern Corridor Medical Engineering – Cardiac Rehabilitation.



The ECME-CR platform consists of the following components:

- The ECME-CR app, a web-based app for guidance, monitoring, and support during the CR exercise class. Participants will interact with the app via a tablet device that will be given to them for the duration of the study. Outside of the CR exercise sessions, participants can also use the app to view data (blood pressure, heart rate, activity, and sleep) from digital devices (Figure 2, Figure 3). Preinstalled educational content relating to exercise and CVD will be accessible to participants on the app at any

time during the intervention period (Multimedia Appendix 1). The design of the app is based on learnings from previous research, including interviews and co-design sessions involving older adults with cardiac conditions [13,14]. Further details of how the ECME-CR app will be used by participants during the exercise classes are outlined below, in the section "Virtual Cardiac Rehabilitation."

- Two off-the-shelf consumer devices, the Withings ScanWatch and the Withings BPM Connect, which are integrated with the platform and used to collect health and well-being data during the virtually delivered CR exercise class as well as during the intervention period. The Withings ScanWatch is a high-end smart watch with an embedded photoplethysmogram sensor for measuring heart rate and oxygen saturation, a triaxial accelerometer for monitoring activity, and electrodes for electrogram recording. The BPM Connect is a clinically validated blood pressure and heart rate monitor. Both devices connect to the Withings Health Mate app via Bluetooth.
- CABIE+, the data collection and aggregation system, which organizes and stores the data acquired from the ECME-CR app and integrated devices.
- SIMS, the information management system, which allows the exercise instructor/research team to view, analyze, and interpret the data collected from the app and the devices in near real time for individual participants (Figure 4).

The CABIE+ and SIMS components of the platform have been described in detail elsewhere [13].

The aim of this pilot trial is to assess the efficacy of a virtually delivered CR exercise program supported by the ECME-CR platform. The effectiveness of the CR intervention will be compared with a control group of individuals who will receive a traditional center-based CR exercise intervention. The primary outcome will be cardiopulmonary exercise capacity as assessed using the 6-minute walk test (6MWT) [15]. The effectiveness of the digital intervention will also be assessed in terms of muscle strength and health-related outcome measures taken before and after the intervention period. The pilot trial will also examine the acceptability and safety of delivering CR exercise classes virtually and will evaluate the usability and acceptability of the digital health platform. Findings from the pilot will inform the feasibility assessment for conducting a full randomized controlled trial.

Figure 2. ECME-CR app dashboard. ECME-CR: Eastern Corridor Medical Engineering – Cardiac Rehabilitation.

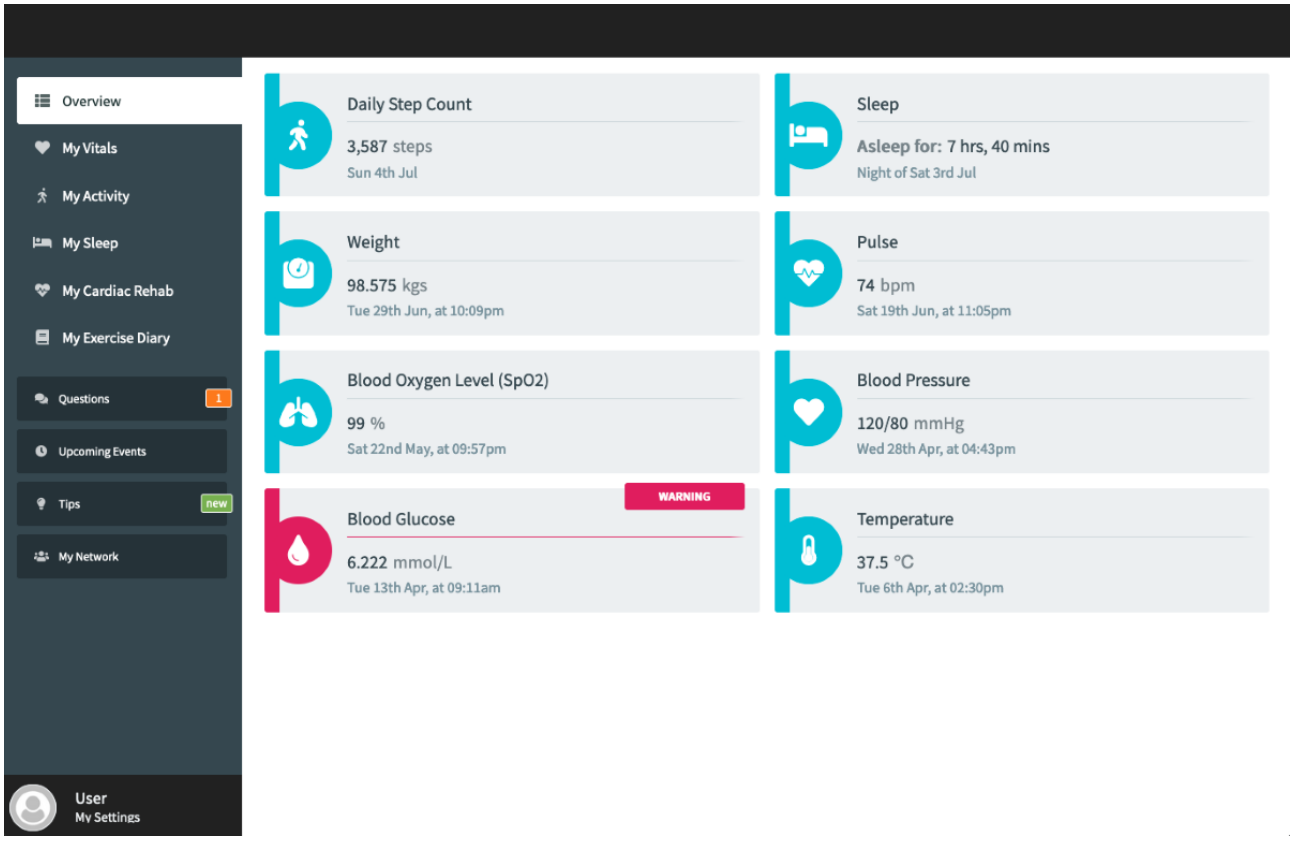


Figure 3. ECME-CR app: view daily average heart rate. ECME-CR: Eastern Corridor Medical Engineering – Cardiac Rehabilitation.

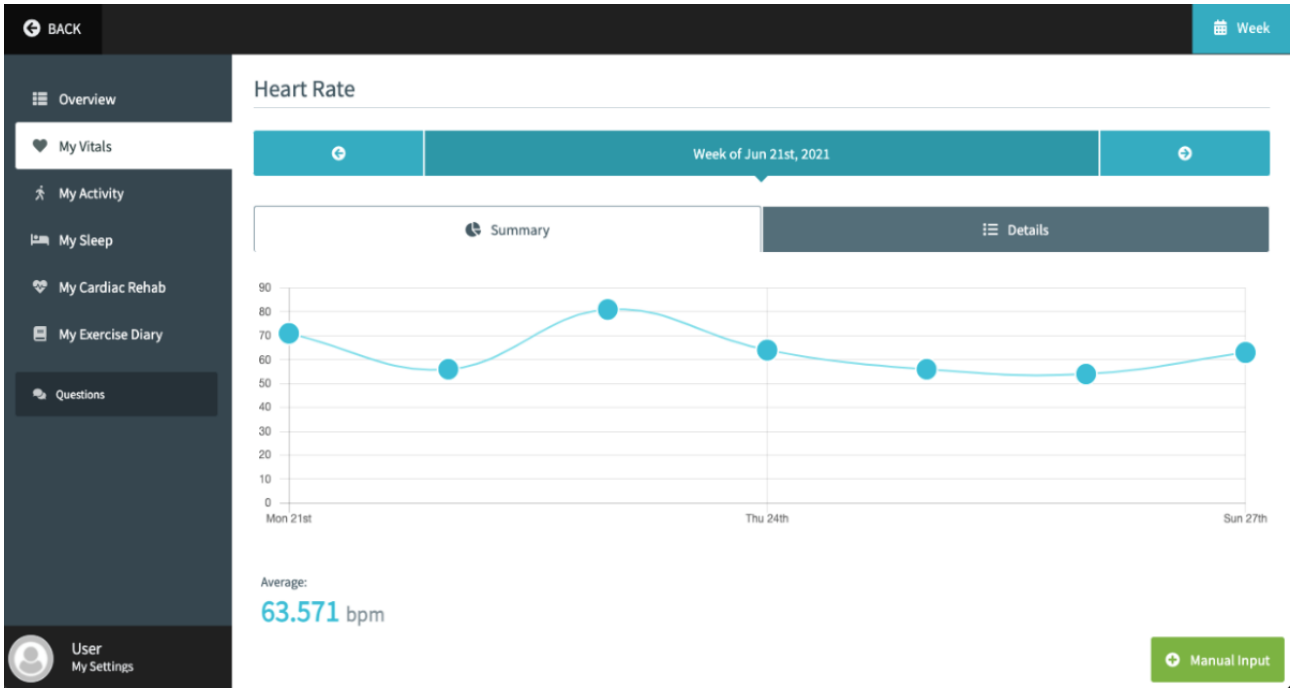
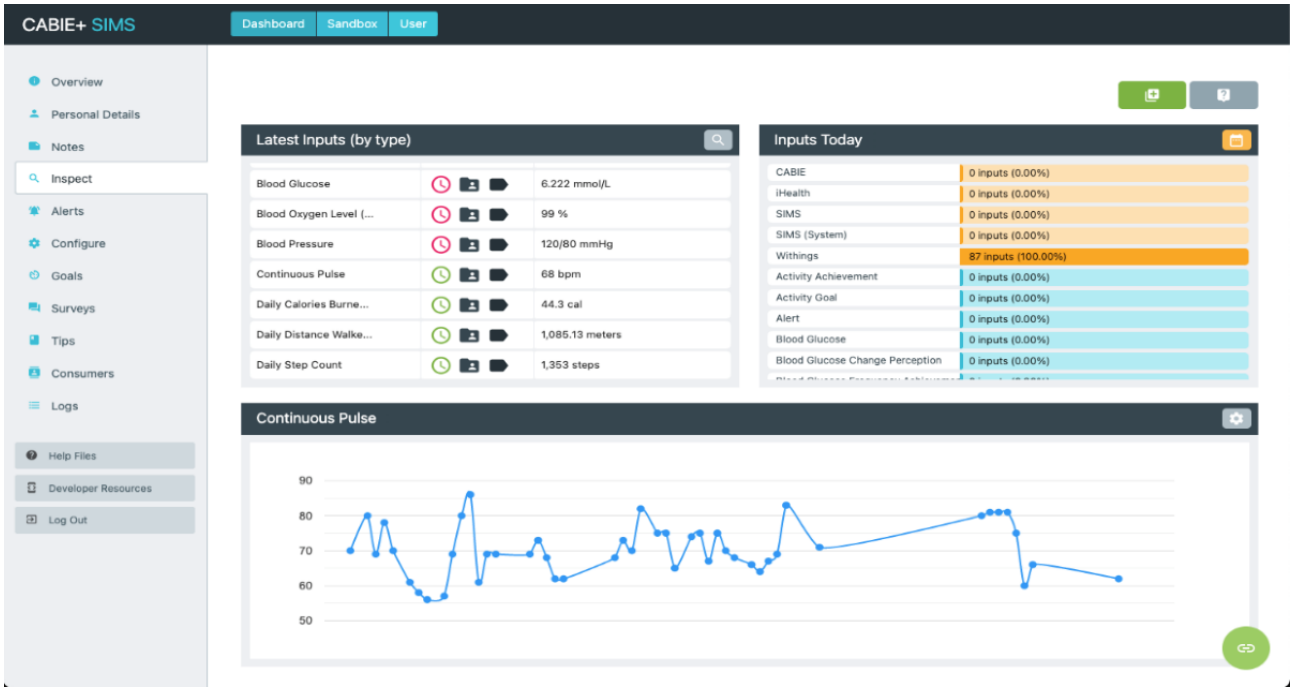


Figure 4. SIMS interface showing inspection of daily heart rate data.



Methods

Study Design

This is a randomized controlled pilot feasibility trial that will examine the efficacy of virtual CR exercise supported by the ECME-CR platform. This study takes an exploratory mixed methods approach and—in addition to the quantitative data generated through the feasibility trial—will generate qualitative data to understand the experiences of participating in virtual CR exercise classes and of using the digital platform.

Ethical Considerations

All study materials and procedures have been reviewed and approved by the Human Research Ethics Committee of Dundalk Institute of Technology. Written informed consent will be obtained from all study participants prior to their participation in the study.

Participants

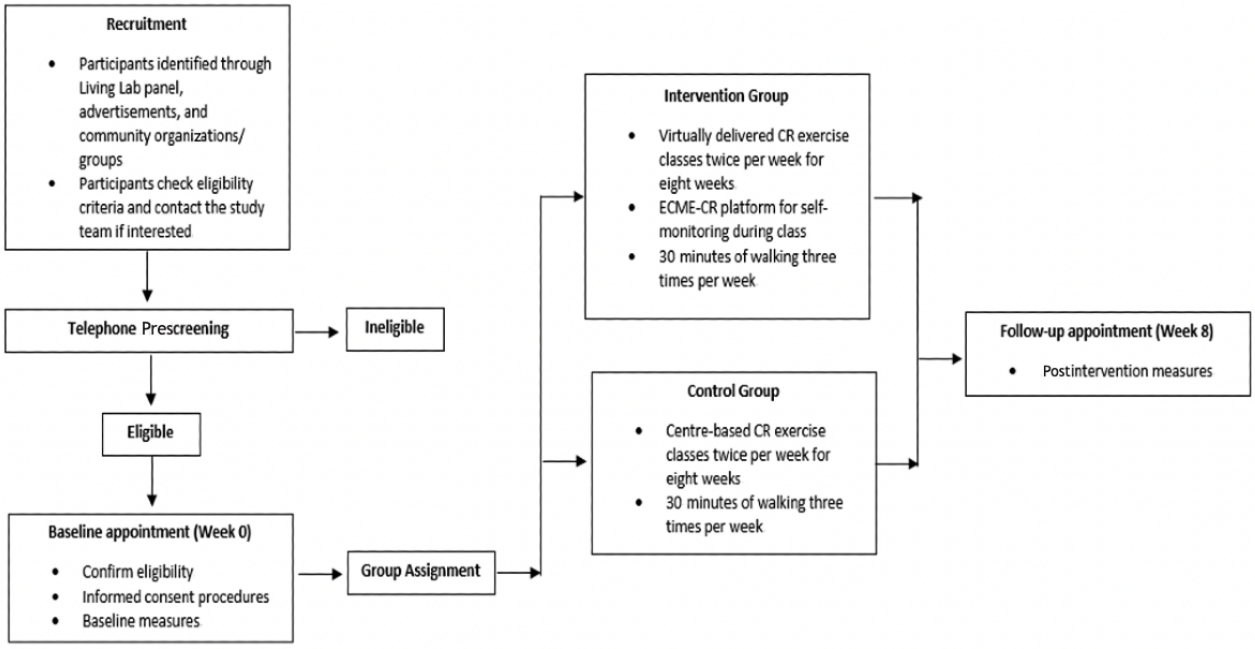
A convenience sample (n=20) of participants eligible to participate in community-based phase IV CR will be recruited. Sample size calculations were not conducted as this is a pilot trial. The sample size of 20 was selected based on the number

of participants that could be conveniently recruited and tested within the pilot study time frame. Participant flow through the study is outlined in Figure 5.

Participants will be recruited from a living lab panel within Dundalk Institute of Technology, and through advertisement in local general practitioner practices, health clinics, and local media, and through community organizations and groups. Potential participants will also be informed of the study while attending outpatient CR sessions in local hospitals. Participants will be asked to contact the study team if interested in taking part. Those that make contact will initially be screened for their eligibility to take part by a member of the research team, over the phone, using the study eligibility criteria (Textbox 1).

Those that are deemed eligible and are willing to participate will then be invited to make an appointment to attend the research center for baseline testing. At this baseline appointment, the researcher will confirm the participant's eligibility and participants will sign the informed consent document should they agree to proceed with the study.

Figure 5. Participant flow through the study. CR: cardiac rehabilitation.



Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Participants will be included if they meet the following criteria:

- Men/women with documented cardiovascular disease eligible to participate in a community-based cardiac rehabilitation program (Phase IV cardiac rehabilitation)
- Aged 40-80 years
- Medically stable with regard to symptoms and no change in pharmacotherapy in the previous 4 weeks
- Clinical approval from their treating physician to enroll in the cardiac rehabilitation program.

Exclusion criteria

Participants will be excluded if any of the following exclusion criteria apply to them:

- Live in a nursing home or other long-term care facility
- Have any contraindications to exercise (adapted from the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription [16]):
  - Unstable angina
  - Uncontrolled hypertension (ie, resting systolic blood pressure >180 mm Hg or resting diastolic blood pressure >110 mm Hg)
  - Orthostatic blood pressure drop of >20 mm Hg with symptoms
  - Significant aortic stenosis (aortic valve area <1.0 cm2)
  - Acute systemic illness or fever
  - Uncontrolled atrial or ventricular arrhythmias
  - Uncontrolled sinus tachycardia (heart rate >120 beats per minute)
  - Acute pericarditis or myocarditis
  - Uncompensated heart failure
  - Third degree (complete) atrioventricular block without pacemaker
  - Recent embolism
  - Acute thrombophlebitis
  - Resting ST segment displacement (>2 mm)
  - Uncontrolled diabetes mellitus
  - Severe orthopedic conditions that would prohibit exercise
  - Other metabolic conditions, such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia (until adequately treated)

Group Assignment

After providing informed consent, participants will be randomly assigned to one of the two study groups. Intervention group participants will follow a virtually delivered CR exercise program in their own home and will receive support via the ECME-CR app. Control group participants will receive usual care only (ie, traditional center-based rehabilitation). Randomization schedules will be generated using a computerized random number generator. To minimize selection bias, an independent researcher will oversee the randomization process. Given the nature of the intervention, it will not be possible to blind the participant nor the outcome assessors to group allocation.

Cardiac Rehabilitation Exercise Program

Overview

Both study groups will perform the same exercise rehabilitation program over an 8-week intervention period. The exercise program will be delivered by a physiotherapist and an exercise therapist with experience in CR exercise, and will consist of 60 minutes of exercise per session with two sessions per week. Each 60-minute session will consist of a 15-minute warm-up, 30 minutes of circuit style aerobic and strength exercises, and a 10-minute cooldown (Multimedia Appendix 2).

Exercise intensity will be assessed during the exercise class by self-report using the Borg scale of perceived exertion [17] and by measurement of heart rate. The level of perceived exertion on the Borg scale should commence at "very light" and gradually progress toward "somewhat hard" during the session [18]. For heart rate, the target range during exercise is 40%-70% of heart rate reserve [18], which will be calculated using the

age-adjusted Karvonen formula [19]. The ScanWatch will be used during the classes to measure heart rate.

At the beginning of each class, participants will be prompted to activate the workout mode on their ScanWatch. The ScanWatch ordinarily takes a measurement of heart rate approximately every 10 minutes; however, when the workout mode is activated, the sampling frequency increases to approximately every three seconds. This high-resolution data will not be available in real time during the class; however, it will be available for review by a member of the research team following the class to assess if the participant was exercising within a safe and effective heart rate. Individualized feedback and tailoring of exercises will be provided to participants based on the postclass review of heart rate data.

During the intervention period, participants in both groups will also be encouraged to undertake additional aerobic exercise (ie, walking) 3 times per week. Participants will be encouraged to progress their activity gradually over the intervention period by first increasing the duration of the activity (ie, covering a greater distance) and then increasing the intensity gradually (ie, increasing the speed of walking). Participants in both groups will self-report the activities undertaken and this data will be included in the analysis. Participants will be guided to include a warm-up and cooldown as part of their activity.

Intervention Group

The intervention group will undertake the exercise program in their own home, joining virtual CR exercise classes. The virtual classes will be delivered using the videoconferencing platform Zoom (Zoom Video Communications Inc), enabling two-way interaction and communication between the instructors and participants. The instructors will guide the participants through the exercise class and will deliver real-time feedback, encouragement, and modifications.

Participants will be provided with a tablet device (10.2-inch iPad Wi-Fi 32GB, 8th generation; Apple Inc) preloaded with the ECME-CR app, the Withings devices, and a set of free weights that will be used during the exercise class. A second tablet device will be provided to participants if they do not have access to their own tablet/PC to join the Zoom CR exercise classes. Intervention group participants will be required to have an established broadband connection in their home; however, if this is not the case, a mobile Wi-Fi device will be given to them for the duration of the study. Participants will receive an equipment familiarization session either in person in the research center or during a home visit, which will include how to operate the tablet and ECME-CR app, how to use the monitoring equipment, and how to record measurements. An equipment manual with written and pictorial instructions will also be supplied.

The ECME-CR app will offer guidance to participants during the exercise class (see Figure 6 for examples of the guidance that will be provided). Participants will also use the ECME-CR app to record exertion levels on the Borg scale as the class progresses (Figure 7). In addition, 5 minutes before each class begins, participants will measure their heart rate and blood pressure at rest using the BPM Connect device. These measurements will automatically synchronize with the ECME-CR app and this data will be available for review by the class instructors on SIMS before the class begins, ensuring it is safe for the participant to exercise. Participants in the intervention group will also use the ECME-CR app to self-report any additional aerobic exercise activities (type, duration, and intensity) undertaken during the intervention period.

Figure 6. ECME-CR app during the virtual CR exercise class. CR: cardiac rehabilitation; ECME-CR: Eastern Corridor Medical Engineering – Cardiac Rehabilitation.

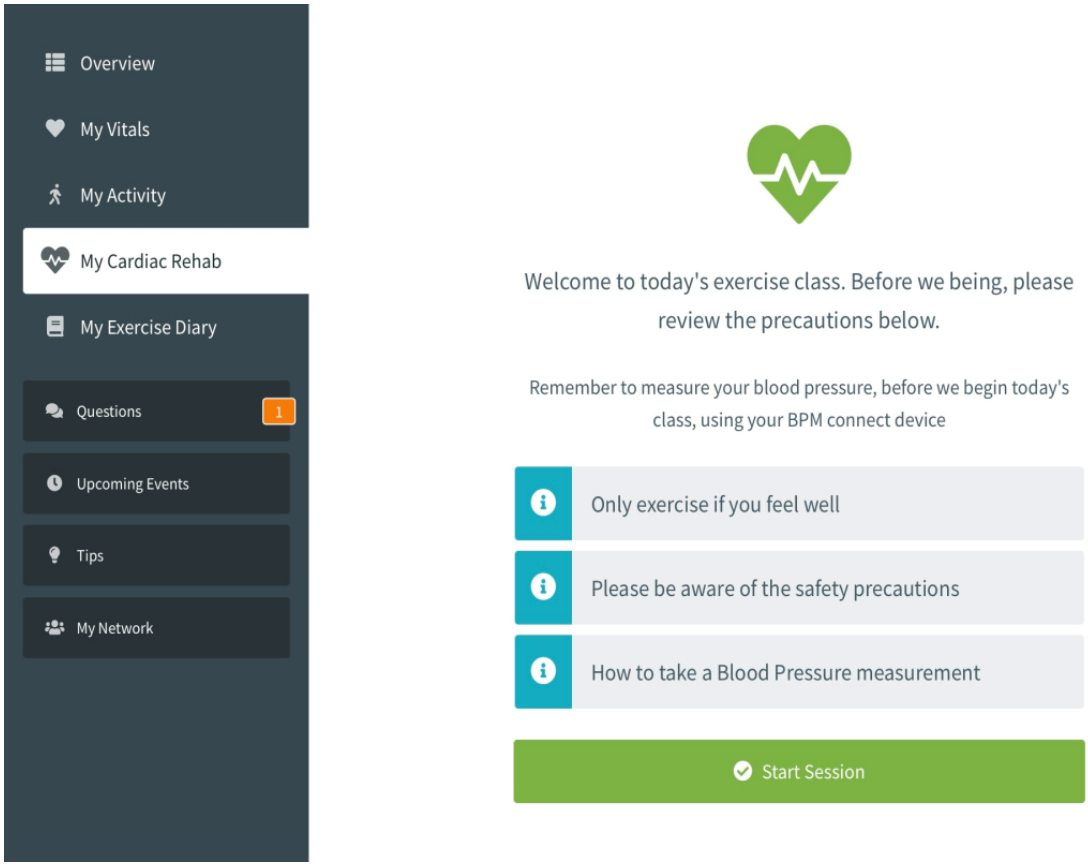
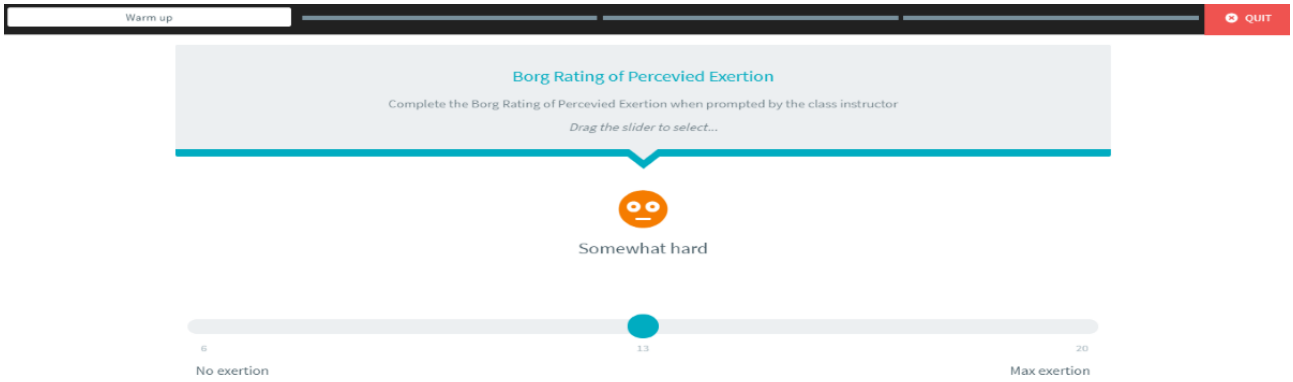


Figure 7. ECME-CR app: recording exertion levels on the Borg scale. ECME-CR: Eastern Corridor Medical Engineering – Cardiac Rehabilitation.



Control Group

The control group will attend the research center to undertake their rehabilitation exercise classes. Each participant's heart rate and blood pressure will be measured at rest using the Withings BPM Connect before beginning the exercise class and again following the cooldown period. Participants will be provided with a ScanWatch to wear for the duration of the class for continuous heart rate measurement. Exertion levels will be monitored at regular intervals and manually recorded by a member of the research team. Participants in the control group will record any additional aerobic exercise activities (type, duration, and intensity) undertaken outside of the classes during the intervention period in a paper diary provided to them.

Outcome Measures

Outcome measures will be assessed at baseline (week 0) and repeated following the intervention period (week 8).

Primary Outcome

The primary outcome will be cardiopulmonary exercise capacity as assessed using the 6MWT [15]. The 6MWT will be performed as per the European Respiratory Society/American Thoracic Society's guidelines [20]. Briefly, the 6MWT will be conducted in a quiet indoor corridor that is flat and straight, with a hard surface. The walking course will be 30 meters in length. The starting line—which marks the beginning and end of each 60-meter walking lap—will be marked with brightly colored tape, while the turnaround point will be marked with a cone.

The 6MWT distance will be recorded to the nearest meter. The test will be performed twice to account for a learning effect [20] and the longer distance will be used in the analysis. Heart rate will be recorded during the 6MWT using the Withings ScanWatch and the data will be synchronized with the Withings Health Mate app.

Secondary Outcomes

Other outcomes will include measurement of strength via measurement of grip strength. Maximum grip strength for each hand will be measured in kilograms using a digital handheld isokinetic dynamometer (Takei 5401, Takei Scientific Instruments Co Ltd). A total of three maximum voluntary grip squeeze contractions will be taken for each hand, alternating between the right and left hand each time. Participants will be assessed in a standardized position and standardized encouragement will be delivered. The best measurement for each hand will be used in the analysis.

Self-reported quality of life will be assessed using a paper-based version of the 12-Item Short Form Survey [21]. Physical health–related outcome measures will be assessed, including measurement of heart rate at rest, blood pressure, weight, and BMI, as well as percentage body fat as measured using the Marsden MBF-6010 Body Composition Scale bioimpedance scale (Marsden Weighing Group) and waist circumference. Heart rate and Borg scale data collected during the CR exercise classes will also be used in the analysis. Participant adherence to the exercise program, engagement with the ECME-CR app and digital devices, and trends in daily physical activity, heart rate, and blood pressure over the intervention period will also be analyzed.

Following the intervention, interviews will be conducted to explore the experience of participating in the virtual CR exercise classes and using the ECME-CR platform. A subset of participants who were assigned to the intervention group will be invited to participate in a semistructured interview conducted either face-to-face, via Zoom, or by telephone. Semistructured interviews will also be conducted with participants in the control group to explore their perceptions of virtual CR exercise classes and what barriers and facilitators may exist to participating in this type of program. An interview schedule will be developed to guide the interviews, which will take approximately 30 minutes. Interviews will be audio recorded and subsequently transcribed verbatim.

Data Analysis

Quantitative data collected at week 0 and week 8 will be collated using Microsoft Excel (Microsoft Corp) and the statistical software package SPSS (version 26; IBM Corp) will be used to analyze the data. Descriptive statistics will be used to describe the data. Data will be presented as frequencies, means, standard deviations, and percentages. Inferential statistical tests (*t* test) will be applied to determine whether there are differences within and between groups following the intervention. The Shapiro-Wilk test will be applied to assess normality and a significance level of $P<.05$ will be applied. Data in SIMS, collected from the app and from the digital devices, will be descriptively analyzed.

The interview transcripts will be coanalyzed by two researchers using NVivo (QSR International) following the thematic analysis process suggested by Braun and Clarke [22].

Results

Participant recruitment and data collection began in July 2021. Dissemination of study results in peer-reviewed journals is expected in spring 2022.

Discussion

Principal Findings

The benefits of participating in CR exercise are well documented, with positive effects for both the individual and the health care system. Despite this, participation rates are low and adherence to CR exercise programs is poor, with many barriers being reported, such as transport difficulties, financial cost, and the lack of program availability [10]. The COVID-19 pandemic has also had an impact on the delivery of CR, with many CR exercise classes being delivered online [12]. Consequently, now more than ever, it is important to develop solutions to support people with CVD to undertake their CR exercise program virtually at home.

In this paper, we present the protocol of a pilot trial that will examine the feasibility of delivering a virtual CR exercise program supported by the ECME-CR platform, a custom-developed digital platform for self-monitoring during CR exercise. We hypothesize that the virtually delivered CR exercise program will result in similar outcomes and will not be inferior to the center-based program. We anticipate that this study will also demonstrate that virtually delivered CR exercise is a safe and acceptable alternative for those who cannot attend or complete traditional center-based CR exercise classes. The sample size in this study will limit the statistical power of the results; nevertheless, as this is a pilot trial, the proposed N is appropriate for meeting the study objectives.

Conclusions

The outcomes of this pilot trial will inform the design of a larger randomized controlled trial that will assess the clinical effectiveness of the ECME-CR digital health platform.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Educational content.
[DOCX File , 31 KB - resprot_v10i10e31855_app1.docx]

Multimedia Appendix 2
Exercise program.
[DOCX File , 23 KB - resprot_v10i10e31855_app2.docx]

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Abbreviations

CR: cardiac rehabilitation
CVD: cardiovascular disease
ECME: Eastern Corridor Medical Engineering
6MWT: 6-minute walk test

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Protocol

Remote Assessment of Lung Disease and Impact on Physical and Mental Health (RALPMH): Protocol for a Prospective Observational Study

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Abstract

Background: Chronic lung disorders like chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are characterized by exacerbations. They are unpleasant for patients and sometimes severe enough to cause hospital admission and death. Moreover, due to the COVID-19 pandemic, vulnerable populations with these disorders are at high risk, and their routine care cannot be done properly. Remote monitoring offers a low cost and safe solution for gaining visibility into the health of people in their daily lives, making it useful for vulnerable populations.

Objective: The primary objective is to assess the feasibility and acceptability of remote monitoring using wearables and mobile phones in patients with pulmonary diseases. The secondary objective is to provide power calculations for future studies centered around understanding the number of exacerbations according to sample size and duration.

Methods: Twenty participants will be recruited in each of three cohorts (COPD, IPF, and posthospitalization COVID). Data collection will be done remotely using the RADAR-Base (Remote Assessment of Disease And Relapse) mobile health (mHealth) platform for different devices, including Garmin wearable devices and smart spirometers, mobile app questionnaires, surveys, and finger pulse oximeters. Passive data include wearable-derived continuous heart rate, oxygen saturation, respiration rate, activity, and sleep. Active data include disease-specific patient-reported outcome measures, mental health questionnaires, and symptom tracking to track disease trajectory. Analyses will assess the feasibility of lung disorder remote monitoring (including data quality, data completeness, system usability, and system acceptability). We will attempt to explore disease trajectory, patient stratification, and identification of acute clinical events such as exacerbations. A key aspect is understanding the potential of

real-time data collection. We will simulate an intervention to acquire responses at the time of the event to assess model performance for exacerbation identification.

Results: The Remote Assessment of Lung Disease and Impact on Physical and Mental Health (RALPMH) study provides a unique opportunity to assess the use of remote monitoring in the evaluation of lung disorders. The study started in the middle of June 2021. The data collection apparatus, questionnaires, and wearable integrations were setup and tested by the clinical teams prior to the start of recruitment. While recruitment is ongoing, real-time exacerbation identification models are currently being constructed. The models will be pretrained daily on data of previous days, but the inference will be run in real time.

Conclusions: The RALPMH study will provide a reference infrastructure for remote monitoring of lung diseases. It specifically involves information regarding the feasibility and acceptability of remote monitoring and the potential of real-time data collection and analysis in the context of chronic lung disorders. It will help plan and inform decisions in future studies in the area of respiratory health.

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KEYWORDS

mHealth; COVID-19; mobile health; remote monitoring; wearables; internet of things; lung diseases; respiratory health; mental health; cardiopulmonary diseases

Introduction

Background

Patients with chronic conditions like chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) must often manage their diseases from a community setting, and this presents natural challenges in monitoring patient health status. Currently, COVID-19 presents additional challenges, especially for vulnerable patients with pre-existing conditions and diseases where, due to shielding, their routine care cannot be performed properly [1]. Remote monitoring of the physiology and symptoms of patients via wearable devices could provide convenient and useful advantages over conventional care for patients managing their health care in real-world settings. These can include detailed information on their historical health, current health status, and potential to intervene during acute events, as well as prognosis of future health and disease trajectory. Remote monitoring may also provide an opportunity during events like the COVID-19 pandemic to safely monitor disease exacerbation or progression without putting patients in situations where risk of exposure to COVID-19 is increased.

Remote Monitoring

This study aims to use the open-source RADAR-Base (Remote Assessment of Disease and Relapse) mobile health (mHealth) platform to collect and analyze multiple data sets associated with respiratory disorders. Several cardiopulmonary parameters are now available in modern consumer wearable devices, and due to close coupling of the heart and lungs, measurements of the functions of these organs are expected to provide good characterization of diseases. This study will include continuous data collected from wearable devices (eg, heart rate [HR], respiratory rate, and oxygen saturation [SpO_2]), including pulse oximeters and spirometers, mobile phones (audio), digital tests, and smartphone symptom questionnaires.

The RADAR-Base community emerged from the Innovative Medicines Initiative (IMI) project RADAR-CNS (Remote Assessment of Disease and Relapse – Central Nervous System), where a consortium of clinicians, developers, researchers, patient organizations, and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners joined forces to explore the potential use of sensor data from wearable devices like fitness trackers and smartphones in research and health care. The RADAR-Base platform is a scalable and interoperable mHealth platform that provides capabilities for remote monitoring passively (eg, sensor data, wearables, and internet of things [IoT]) and actively (eg, questionnaires and digital tests). The platform developed at King's College London and the Hyve in the Netherlands is already being used in a number of large-scale longitudinal mental and physical health–related disorder projects [2,3]. The complete RADAR-Base technology stack is available under an Apache 2 open-source license and is supported by an active community of developers, researchers, and clinicians who focus on continuously improving data quality, user experience, and validation, and extending the platform with new features and data sources.

All the data collected and aggregated using the RADAR-Base platform are standardized using Avro schemas [4] and harmonized across various data streams.

RADAR-Base also provides the potential to respond or alert in near real time based on some state of the data being collected; this could include identifying, for example, an exacerbation and triggering a response, such as an intervention or follow-up questionnaire/test or confirmation.

This pilot will help answer how remote monitoring may be used for lung disease patients, who in many cases may be shielding during the COVID-19 pandemic because of being at high risk and being vulnerable, and offers additional benefits, including participation without additional risk of travel or interaction with hospital staff.

ILD

ILD, or lung fibrosis, is one of a spectrum of fibrotic diseases associated with aging, obesity, diabetes, and pollution, which

are responsible for approximately 45% (9/20) of premature deaths in Western Europe. Of over 90,000 patients in the United Kingdom with ILD, approximately 30,000 have idiopathic pulmonary fibrosis (IPF), which is the most severe form. IPF is a disease of unknown etiology that is more frequent in males and presents mainly in the sixth and seventh decades of life [5]. There is no cure, and the median survival of 3 to 5 years following diagnosis is worse than that for many cancers. As the fibrosis progresses, there is impaired pulmonary function, respiratory failure, and ultimately death. Throughout its course, IPF has significant effects on physical (dyspnea, dry cough, weight loss, and fatigue) and social (recreational activities and relationships) functions, with severe consequences for the patient's health-related quality of life (QoL). Clinical courses are punctuated by episodes of worsening disease that may result in death. These acute exacerbations of IPF (AE-IPF) are estimated to occur in 4% to 20% (1-4 in 20) of patients each year, but the true incidence and impact are not known [6].

Management of AE-IPF involves establishing the diagnosis and excluding other causes of increasing dyspnea, excluding infection, and considering the use of steroids, antibiotics, and/or anticoagulation, none of which has been shown to be of benefit. The trajectory of patients with IPF is heterogeneous with great variability in the disease course. Some progress slowly, whereas others progress more rapidly, and this can cause emotional distress and anxiety. Patient-reported outcome measures are used to measure health-related QoL, assess symptoms, and evaluate disease progression. The management of patients with IPF is multifaceted and consists of patient education and support, regular outpatient surveillance, symptom relief, pulmonary rehabilitation, annual vaccinations to prevent respiratory infection, identification and management of AE-IPF, supplemental oxygen, management of comorbidities, and ultimately palliative care or, in a minority of patients, referral for lung transplantation [7].

Two antifibrotic treatments (pirfenidone and nintedanib) are available for patients who meet the stringent National Institute for Health and Care Excellence (NICE) criteria. They neither cure nor reverse the fibrosis and have little impact on symptoms, but they have been shown to reduce the rate of lung function decline, and pirfenidone has been shown to reduce AE-IPF and improve progression-free survival [8].

With regard to the impact on health care systems, IPF is a cost- and resource-intensive disease encompassing hospitalization, home care, long-term care, and antifibrotic therapy. The full health burden on the National Health Service (NHS) and UK economy is unknown, but data from the British Lung Foundation and projected estimates from our patient cohort suggest that there are approximately 30,000 IPF diagnoses each year. Health care costs alone for IPF are estimated at US $15,000 to $78,000 per patient-year [6].

Regarding the need for biomarkers for precision management, the disease progression in IPF is highly variable with individuals experiencing very different trajectories. Response to antifibrotic therapy is also inconsistent with some patients tolerating the medication well and others experiencing significant side effects. Currently, there is a lack of valid endpoints, apart from a change in forced vital capacity, which has poor sensitivity and specificity to accurately assess disease activity or response to treatment [9]. This makes it difficult to predict individual prognosis or reliably detect early treatment response or failure, which is important for developing treatment plans and providing patients with accurate prognostic information, which allows them to plan for their future. Remote monitoring may allow clinicians and patients access to more granular longitudinal data on disease progression, the rate of AE-IPF, and effects on QoL, and begin to offer personalized treatment approaches in this cohort. Remote monitoring may also reduce patients' attendance at the hospital for clinical follow-up or when taking part in clinical trials of novel agents. Remote monitoring may allow the early identification of AE and a better understanding of the frequency and impact of these events, and may provide the potential to develop clinical trials of treatments in these patient groups.

COPD

COPD is a common long-term condition of the lungs that is usually caused by cigarette smoking. In addition to daily symptoms and limitations in activities, patients are prone to developing chest infections called "exacerbations" [10,11]. Exacerbations are a significant problem. They are unpleasant for patients and sometimes severe enough to cause hospital admission (and therefore NHS pressures) and death. Reducing the impact of exacerbations is very important [12]. We have previously shown that earlier treatment of COPD exacerbations results in faster recovery and reduced chance of hospital admission. Helping patients to detect exacerbations early is therefore important. We have also recently shown that monitoring HR and oxygen saturation via a finger probe may assist in this, especially overnight when the physiological signal is cleaner [13]. Integration of these signals with additional symptom data and use of innovative data analysis methodology are likely to result in the greatest chance of supporting the early detection of exacerbations and assessment of disease progression. This is even more important in the era of COVID where many patients with COPD are classified as "clinically extremely vulnerable," and thus, remote monitoring provides the safest way to support management in partnership with their clinicians.

Posthospitalization COVID-19 Lung Disorders

Recovery from COVID-19 has many unknowns, especially in the long term [14]. The symptoms of COVID-19 have varied among those who have tested positive. Some have displayed no symptoms, while others have developed severe pneumonia, progressing to lung injury, and acute respiratory distress syndrome, as well as pulmonary fibrosis in the longer term. Notably, the consequences of COVID-19 include effects on other organs, including the heart, kidneys, and brain. Correspondingly, a diverse set of associations have been observed that together have been called "long COVID," which involves prolonged and delayed recovery from the acute illness, including fatigue, shortness of breath, and cough, associated with mental health and neurological disorders, such as fatigue, trauma, and anxiety/depression [15,16]. For those who were hospitalized and have since been discharged, it is not yet clear

what their medical, psychological, and rehabilitation needs will be to enable them to make as full a recovery as possible.

Given this need to follow-up with COVID-19 patients after hospitalization, we consider remote monitoring to provide some key opportunities. First, observation of chronic symptoms will necessitate home-based monitoring, as the scope of regularly interfacing with participants in the clinic may be limited due to the likelihood of further periods of lockdown and self-isolation of this population. Second, there needs to be a greater focus on understanding how daily life is affected by this disease. Remote monitoring, therefore, provides an ideal opportunity to collect multiple continuous data streams from participants to report on physiology, QoL, and environmental and functional aspects. Building on our existing experience in using wearables to monitor participants who develop COVID-19 [17], we aim to extend this to enable detailed observation of patients as they experience symptoms of long COVID. By using a longitudinal, high frequency, and largely passive monitoring approach, we aim to develop an understanding of the disease trajectory and the fluctuation of symptoms.

Theoretical Framework

The Remote Assessment of Lung Disease and Impact on Physical and Mental Health (RALPMH) study will use a prospective cohort study framework. This will leverage our RADAR-Base software platform and existing experience working on remote monitoring projects, such as RADAR-CNS [18], and take a similar approach to the major depressive disorder protocol [19]. In addition to this, we have recently developed RADAR-Base capabilities to deliver notifications dependent on real-time processing of participant data streams. This module of RADAR-Base will be evaluated here by deploying an exacerbation detection algorithm (using HR, SpO_2, and other measures), and participants will be asked in near real time to confirm/reject and score the algorithm's assertion via a short questionnaire, the Exacerbation Rating Scale (ERS), close to or during the period of exacerbation, in order to provide accurate feedback independent of recall. The ERS scoring will be used to evaluate the algorithm sensitivity/specificity and to evaluate options for personalized exacerbation detection.

Previous studies [12,13] on exacerbations in COPD found that changes in resting heart rate (RHR), pulse oxygen saturation (SpO_2), and peak airflow are highly correlated with symptoms before, during, and after exacerbation onset, as shown in Figure 1.

Another study [20] looked at the identification and subsequent prediction of exacerbations in COPD. The authors used features derived from pulse oximeters to predict exacerbations using logistic regression. They found that all three vital signs (oxygen saturation, pulse rate, and respiratory rate) are predictors of exacerbations, with oxygen saturation being the most predictive. Another study [21], which looked at the correlation between RHR and acute exacerbations in COPD, found that patients with a higher RHR following exacerbation demonstrated an increased risk of exacerbation.

There is evidence in the literature that pulmonary diseases, like COPD, lung fibrosis, etc, are closely related to the heart [22]. Pulmonary vascular abnormalities are frequently present in patients with respiratory disorders. Similar correlations were found with HR in severe acute respiratory syndrome (SARS), where patients were found to have a high HR and low blood pressure [23].

One interesting and relatively novel approach to understanding the changes in respiratory disorders is through capturing breathing sounds to measure the breathing rate and detect features such as wheezing, coughing, sneezing, and snoring, using audio data. Two exciting works in this field are mLung++ [24] and SonarBeat [25].

The mapping between data types and analytical approaches under consideration is shown in Table 1.

Figure 1. Time course of symptoms and oximetry variables at exacerbation [11]. PEF: peak airflow.

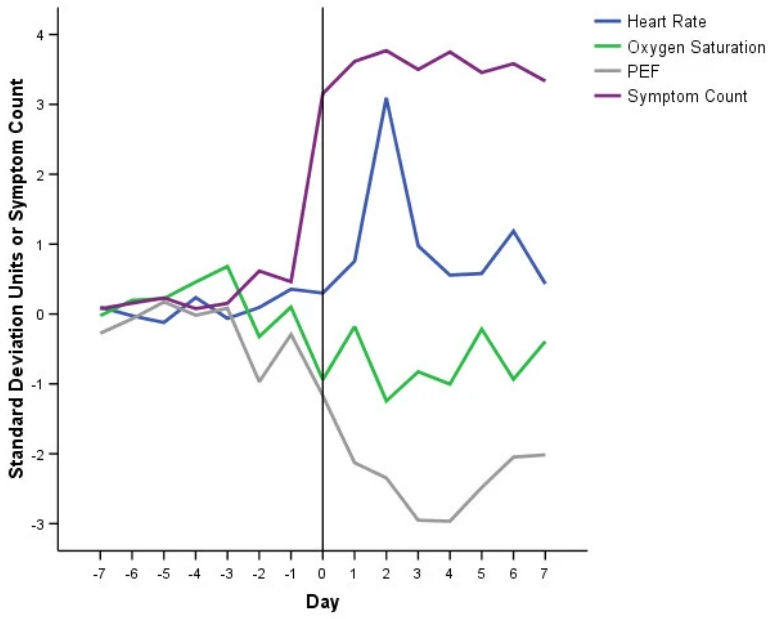


Table 1. Data analysis methods.

Data type	Methods	Labels
Active raw audio	MFCC[a], SVM[b], Adaboost	Questionnaires, tasks, spirometry
Passive wearable sensor	KNN[c], least squares regression, Adaboost, HMM[d]	Questionnaires, tasks, event diary, spirometry
Multimodal sensor	DeepSense (CNN[e]+RNN[f]), GIR[g], hierarchical HMM	Questionnaires, tasks, spirometry

[a]MFCC: mel-frequency cepstral coefficients.

[b]SVM: support vector machine.

[c]KNN: K-nearest neighbor.

[d]HMM: hidden Markov model.

[e]CNN: convolutional neural network.

[f]RNN: recurrent neural network.

[g]GIR: global iterative replacement.

Aims

Our goal is to investigate the acceptability and feasibility of remote monitoring of patients with pulmonary disorders for the quantification of symptoms, understanding of the disease trajectory, and detection and prediction of clinically important events, such as exacerbations, in the following three disorder areas: COPD, ILD, posthospitalization COVID.

Objectives

Primary Objective

The primary aim of the study is to evaluate cardiopulmonary disorders as potential targets for real-time, continuous, real-world remote monitoring. This study will investigate the potential benefit, acceptability, and feasibility of multiparametric remote monitoring of patient symptoms and physiology using commercially available wearable sensors for HR, activity, and SpO_2; spirometry; phone sensors; questionnaires; and digital tests in patients with a range of pulmonary disorders.

The evaluation will be based on patient acceptability, dropout rates, and interpretation of data; detection of clinically important events, such as exacerbations and disease progression; quantification of symptoms (physical and mental health); impact of the disease on mood and well-being/QoL; and trajectory tracking of main outcome variables, symptom fluctuations, and order.

Secondary Objective

The secondary objective of this study is to provide data for power calculations [26] for a follow-on study. Power calculations will be centered around understanding the number of exacerbations according to sample size and duration. The power is effectively how good the signal is.

This will help plan future studies where we need to decide the sample size and duration to obtain accurate and acceptable exacerbations and the data associated with them.

Outcomes

Acceptability of the Remote Monitoring System in the Three Disease Areas

The acceptability of the platform will be determined in terms of recruitment, retention, data completeness, and the qualitative experience of participants. The exit survey Technology Assessment Model Fast Form (TAM-FF) will also be used to evaluate the data collection infrastructure with participant feedback. The study will test both the feasibility and acceptability of tasks for participants. On completion of the data collection period, we will measure the total available data as a function of a theoretical maximum and assess data quality measured by a range of criteria, including missingness and contiguity.

Assess the Potential of Remote Monitoring in COPD, IPF, and COVID-19

The potential of remote monitoring will be evaluated in the context of cardiopulmonary disorders. This will involve developing methods to quantify disease trajectory as compared with standard clinical measures (in IPF, these would be changes in forced vital capacity and death); detecting exacerbations/symptoms, such as changes in wearable data (eg, HR, SpO_2, and activity), during the reported period of exacerbation (a real-time algorithm will be included to predict exacerbations with patients notified with the ERS to confirm the prediction at or close to the time of the event); detecting exacerbations prior to or after the reported period of exacerbation (eg, a signal that may precede participant awareness of the exacerbation/symptom); detecting subclinical exacerbations in patients with lung fibrosis; tracking self-reported symptoms and outcomes (including precursor presymptomatic signals) and their frequency and order; and reporting longitudinal mental health symptom measures, as reported by the Generalized Anxiety Disorder scale (GAD-7) and Patient Health Questionnaire depression scale (PHQ-8), associated with the three diseases. This will provide the potential to assist with future applications around disease self-management. In the case of the posthospitalization COVID cohort, we will assess whether remote monitoring can be used as a symptom collection tool and as a long-term low-burden monitoring solution. Fatigue will be assessed by Garmin Body

Battery values and the Fatigue Severity Scale, while long-term COVID impairments will be measured weekly using the Centers for Disease Control and Prevention (CDC) COVID-19 long-term effects (CCLTE) list, World Health Organization (WHO) symptoms list, and post-COVID functional status (PCFS), a COVID-19-specific widely used questionnaire on health-related impairments (physical functioning scale).

Data for Future Calculations

This study will provide data and information for future power calculations for larger cohort studies, including informative data types established by analysis of correlates with symptoms or outcomes of interest. An informative minimal data set can then be derived from this superset. This will also provide the unit cost of data collection for the full and minimal data sets for the planning of any future studies.

Remote monitoring provides the opportunity to continuously monitor patients in their daily lives outside of the hospital, with the potential to automate the detection of disease exacerbations and monitor the long-term evolution of disease trajectory. The acceptability and feasibility of remote monitoring using measures of heart and lung functions in patients with lung diseases are necessary first steps in this process, which this study aims to evaluate.

Methods

Study Design: Methods of Data Collection

RADAR-Base mHealth Platform

Active Data Collection

The Active Remote Monitoring Technology (aRMT) app (Android and iOS) will be used to collect data from patients by issuing questionnaires and tests that require some conscious action to perform. These will include questionnaires for participant QoL and mental health (GAD-7 and PHQ-8) and disorder-specific questionnaires for symptom tracking of COPD (COPD Assessment Test), ILD (Living with Idiopathic Pulmonary Fibrosis assessment), and posthospitalization COVID (PCFS, CCLTE list, and WHO COVID-19 symptoms list). These are summarized in Table 2. Participants will be issued a notification (at the appropriate time) that will open the corresponding questionnaire to be filled on the mobile app. Further to the scheduled questionnaires, the app will be used to generate dynamic notifications for questionnaires to validate the performance of symptom classification and prediction in near real time. Details of the aRMT mobile app are provided in Figure 2.

This study will also include a battery of experimental digital tests to explore the potential to assess lung breathing function through the use of audio capture or other interactive means. Audio data are readily available through the phone's built-in microphone (or the addition of an auxiliary Bluetooth microphone for improved or standardized sound capture). Participants will be issued a notification to complete the relevant task, and selecting this will open the corresponding test on the mobile phone with instructions on how the test is to be performed. Active audio tasks, such as pronouncing sustained vowels and counting from 1 to 20, will provide additional information on voice production dynamics that might be affected by lung disorder symptoms. A lung sound test, which will record audio during breathing by placing the microphone against the chest during a sequence of breaths [42,43], might be evaluated in a further study based on this protocol.

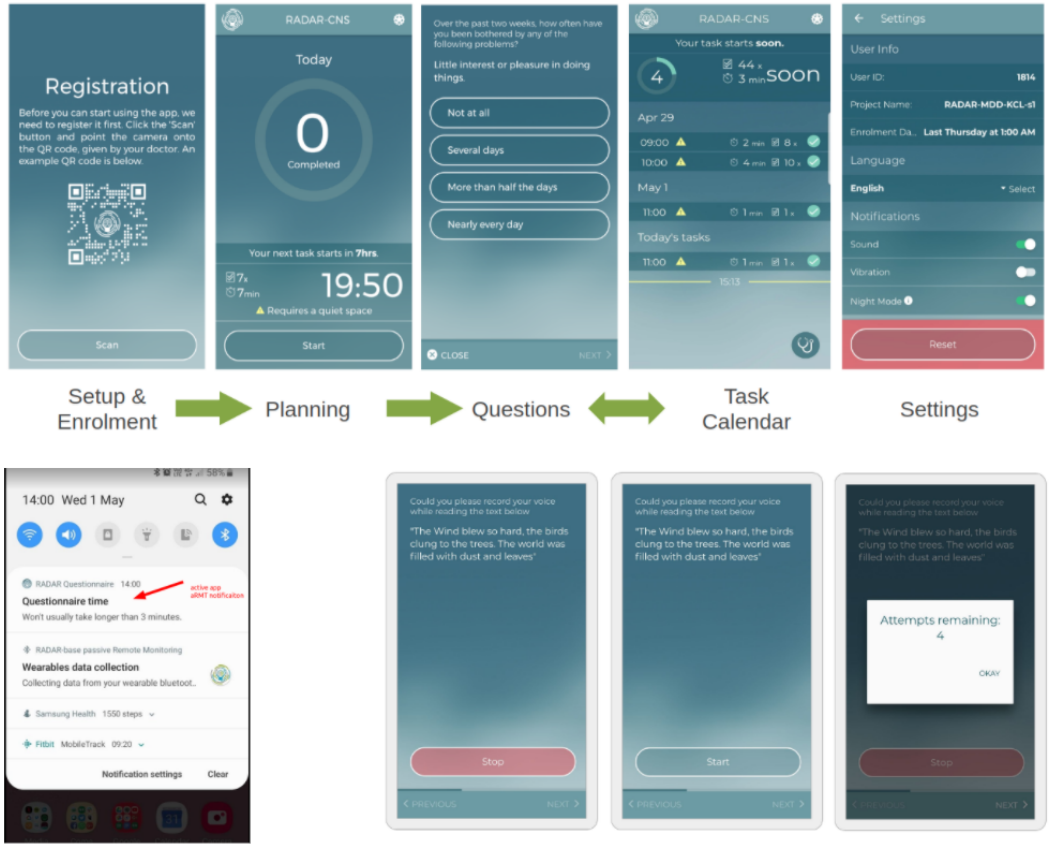
Furthermore, the audio tasks will be validated in conjunction with patient tests and protocol development to ensure that they capture relevant information. Quality assurance mechanisms will be implemented to ensure that incoming audio signals are valid (eg, checking if the signal-to-noise ratio is within an acceptable scope or if the voice is contained within a sample).

Table 2. Remote monitoring measures.

Remote monitoring parameter	Data source	Collection frequency	Cohort	Purpose
Speech and audio				
Speech – Active Remote Monitoring Technology (aRMT)	Digital test/aRMT phone app	Weekly	All	Voice production tasks via the phone. These tasks will assess change in the phonatory-respiratory system [3].
Activity, functioning, and fatigue				
Activity	Wrist wearable device	Continuous	All	Measure exercise levels, and combine and compare heart rate (HR) for the measurement of proportional nonresting HR. Impacts on lifestyle, including physical activity and mobility [27].
Sleep parameters	Wrist wearable device	Continuous	All	Evaluation of the duration and quality of sleep [28].
Fatigue severity scale	Questionnaire/aRMT phone app	Weekly	All	Subjective experience of fatigue [29].
Passive fatigue measure	Wrist wearable device	Continuous	All	Heart rate variability (HRV), time to bed, and Garmin Body Battery level [30,31].
Cardiopulmonary				
HR	Wrist wearable device	Continuous	All	Continuous measure of baseline HR for (1) resting HR (sedentary and sleeping), (2) nonresting HR (under light, medium, and high activity or stair climbs), and (3) cardiopulmonary performance [32].
HRV	Wrist wearable device	Continuous	All	Continuous measure of the variation in time intervals between consecutive heartbeats. Low resting HRV is an indication of high levels of physical or mental stress [33].
Respiratory rate	Wrist wearable device	Continuous	All	Respiration rate [34].
Pulse oximeter (SpO_2)	Wrist wearable device (continuous)	Continuous (nighttime)	All	Blood oxygenation as measured by PhotoPlethysmoGram sensors on the wrist wearable device; this measurement should be continuous at least during the nighttime [35].
Pulse oximeter (SpO_2)	Finger pulse oximeter (periodic)	Daily	All	Periodic assessment with a clinically approved finger-worn device will be provided to validate the daily measure and may be included for dynamic spot checks.
Breathing	Digital test/aRMT phone app	Weekly	All	Measure lung function and volume by inspiration and expiration using tests delivered through the aRMT app and audio capture.
Spirometry	Spirometer	Daily	All	Lung function measurement.
Questionnaires - Symptoms, mental health, quality of life (QoL) (aRMT)				
Post-COVID-19 functional status (PCFS) scale	Questionnaire/aRMT phone app	Weekly	COVID-19	Establish post COVID-19 functional status [36].
CDC COVID-19 long-term effects (CCLTE) (aRMT)	Questionnaire/aRMT phone app	Daily	COVID-19	Establish the degree of long-term COVID-19 effects [15].
WHO COVID-19 symptoms (WCS) list (aRMT)	Questionnaire/aRMT phone app	Daily	COVID-19	Establish the degree of persistent COVID-19 symptoms [37].
COPD assessment test (CAT)	Questionnaire/aRMT phone app	Cohort: Daily	All	CAT to measure the impact of COPD on a person's life. It is unidimensional, and assesses cough, sputum, dyspnea, and chest tightness. Eight questions [38,39].
Idiopathic pulmonary fibrosis patient-reported outcome measure	Questionnaire/aRMT phone app	Weekly	Interstitial lung disease (ILD)	ILD QoL self-report.
Living with idiopathic pulmonary fibrosis	Questionnaire/aRMT phone app	Daily	ILD	ILD QoL self-report.

Remote monitoring parameter	Data source	Collection frequency	Cohort	Purpose
Visual analog scale (VAS) cough	Questionnaire/aRMT phone app	Monthly	ILD	Score symptoms (cough).
St. George's Respiratory Questionnaire (SGRQ)	Questionnaire/aRMT phone app	Quarterly	All	Assess the impact of overall health, daily life, and well-being in patients.
Pittsburgh Sleep Quality Index (PSQI)	Questionnaire/aRMT phone app	Monthly	ILD	Sleep scoring questionnaire.
Exacerbation rating scale (ERS)	Questionnaire/aRMT phone app	Dynamic/on demand	All	A confirmatory rating scale for detected exacerbations in real time; participants will be sent notifications to complete these.
Generalized Anxiety Disorder scale (GAD-7) and Patient Health Questionnaire depression scale (PHQ-8) (aRMT)	Questionnaire/aRMT phone app	Fortnightly	All	Establish depressive and anxiety symptoms [40,41].
Electronic case report form (eCRF) and surveys				
Epworth sleepiness scale	eCRF REDCap	Baseline	All	Used to diagnose obstructive sleep apnea (OSA).
STOPBang questionnaire	eCRF REDCap	Baseline	All	Used to diagnose OSA.
MRC breathlessness	eCRF REDCap	Baseline	All	Dyspnea scale that is used to evaluate the impact of breathlessness on daily activity.
Demographics	eCRF REDCap	Baseline	All	Patient demographics form.
Study information	eCRF REDCap	Baseline	All	Study-related information collected at baseline, for example, phone and device registration, and administrative information.
Contact information	Local Site File	Baseline	All	Contact information.
Technology Assessment Measurement Fast Form	eCRF REDCap	End of study	All	Measure the impact of the technology being used and evaluate its acceptability, usability, and performance.
Experience of participation	eCRF REDCap	End of study	All	Exit interview (semistructured).

Figure 2. The Active Remote Monitoring Technology (aRMT) app used to collect phone-delivered questionnaires. Top: app screens and example questionnaire. Bottom left: Example notification to complete the questionnaire. Bottom right: Speech task.



Passive/Background Data Collection

Garmin Vivoactive 4 is the selected wrist-worn wearable device. Several parameters of interest are reported continuously by the wearable device, including activity (steps and exercise as calories consumed), sleep, fatigue, HR, fatigue levels (Garmin Body Battery), HR variability, respiratory rate (RR), and pulse oximetry (SpO_2) (Table 2).

Additional periodic data collection will be done with finger pulse oximetry and spirometry (Table 2). Participants will receive a notification to carry out pulse oximeter and spirometry tests at a convenient time on a daily basis, and values will be recorded on the aRMT app.

Data Sources

Data sources used in this study include wearable devices, mobile phone apps, and questionnaires. All the measures collected are shown in Table 2.

Clinical Data

Participants will be requested to consent to their medical records (routine clinical and GP records; via the clinical team) and anonymized data being made available to the study team throughout the study. Where possible, specific data sets from routinely acquired clinical records may be included.

Data Analysis

Multimedia Appendix 1 summarizes the data analysis algorithms and models under consideration in this study.

Analyses are intended to assess the feasibility of the RADAR-Base platform for lung disorder remote monitoring (including the quality of data, the cross-section of passive and active data, data completeness, the usability of the system, and the acceptability of the system).

We will generate descriptive statistics for demographics, attrition rate, and the number of participants using the remote assessment measurements without loss or damage and providing adequate quantity and quality of data, and for the duration of the study period.

Using classification/regression/machine learning approaches, we will investigate whether any demographics and/or other numerical information obtained during the baseline and longitudinal data collection periods of the study might serve as predictors for subject dropout and the percentage of adequate data.

We will establish the appropriate setup of data collection and the parameters of the study, which would be required to conduct a future larger longitudinal study.

Feasibility and acceptability of the wearable device will be assessed by answering the following questions: (1) Are the sensors on the device (not a gold standard) feasible and acceptable to conduct remote monitoring of pulmonary diseases? (2) Is Garmin a feasible device for measuring changes in key physiological parameters such as HR and SpO_2? These will be evaluated against the gold standard device (pulse oximeter and spirometry).

The feasibility of the symptom questionnaire will be evaluated against the gold standard from spirometry. Technology Assessment Measurement Fast Form (TAMFF) plus the experience of participation exit interviews will be used to determine the overall feasibility and acceptability of the technology and the protocol used in the study.

If adequate data are collected in the pilot, we aim to explore methods to establish the feasibility of the data collection apparatus as a means to study disease trajectory and patient stratification.

This will involve using data involving HR, SpO_2, sleep, activity, respiratory rate, questionnaires, and other collected measures to model participant stratification and differential disease trajectory.

We will explore the identification of acute clinically interesting events, such as exacerbations and rapid changes in clinical conditions or physiological data streams.

We will use the pulse-respiration quotient [44] and pulse-activity quotient as measures of the changes in respiration efficacy and exacerbation.

We will adopt machine learning approaches to perform both cross-sectional and individualized classification for the identification of events, such as exacerbations, using a questionnaire or other active data as labels providing context to passive data streams such as HR, SpO_2, respiratory rate, and others.

Using multimodal data sets, we will characterize the periods of time around acute events, such as exacerbations, to include the pre-exacerbation period, period during exacerbation, and postexacerbation period.

We will investigate the potential of the data collected to identify putative subclinical exacerbations or other lower level fluctuations in participant symptoms.

If adequate numbers of events are generated in the study, an opportunity to apply anomaly/novelty detection methods will be possible. In this way, we will use these approaches to learn the baseline state for the participants and establish significant deviations from this.

Using the real-time aspect of the data collection, we will use the real-time ERS to acquire real-time responses to evaluate and assess the performance of a model for exacerbation detection and refine an individual-level model for exacerbation detection.

Since we do not have enough prior data, we plan to consider real-time anomaly detection methods and preprocess the data based on prior knowledge. The models will be pretrained on a daily schedule (using previous N days of data; N is yet to be decided but is initially considered 21 days) and will be ready for running inferences in real time (using wearable sensor data as inputs collected in real time) and taking actions based on the results of the inferences (sending an ERS assessment through the aRMT app) to acquire responses at the time of the event to assess the performance of the model.

Study Setting

The main study setting will be remote and will involve near real-time home-based monitoring, and data will principally be collected under this setting. Participants will also attend baseline and exit face-to-face visits with the clinical team, during which initial baseline and exit data will be obtained and assessments will be conducted.

Sample and Recruitment

Inclusion Criteria

The inclusion criteria are presented in Table 3.

Table 3. Inclusion criteria.

Criteria	COPD[a]	ILD[b]	PH-COVID[c]
Clinical conditions	20 patients with a diagnosis of COPD	20 patients with a diagnosis of ILD	A clinical diagnosis of COVID-19 (within 4-13 weeks of enrollment) who report symptoms interfering with day-to-day activity present for more than 28 days following the onset of COVID-19
Gender	Male/Female	Male/Female	Male/Female
Age range (years)	18+	18-90	18+
Prior mobile phone use	Required	Required	Required
Willingness to use monitoring devices and complete study questionnaires	Required	Required	Required
History of exacerbation	2 or more exacerbations in the last 1 year	N/A[d]	N/A

[a]COPD: chronic obstructive pulmonary disease.

[b]ILD: interstitial lung disease.

[c]PH-COVID: posthospitalization COVID.

[d]N/A: not applicable.

Exclusion Criteria

The exclusion criteria for all groups (COPD, ILD, and posthospitalization COVID) are as follows: non-English language speaker, lack of physical capability to participate (eg, heart failure), pregnancy, and lack of capability to consent.

Sampling

Convenient sampling will be employed for this pilot study.

Sample Size

The study will include 20 participants for each of the three disease areas. This is a small sample feasibility study to assess the practical use of remote monitoring in three lung disease areas. The sample size will adequately allow objective assessment of the system deployed for this type of data collection in the typical patient population.

Sampling Technique

Sequential participants who fit the inclusion/exclusion criteria will be identified from the respiratory outpatient clinics at the University College London Hospital (UCLH) and Royal Free Hospital (RFH).

Recruitment

Participants who fit the inclusion/exclusion criteria will be identified from the respiratory outpatient clinics at the UCLH and RFH.

Sample Identification

Participant Search and Consent

Recruitment will be done either in person (via a cleanroom) or remotely (by phone or video call) by clinicians, who will provide information about the study in an easily accessible form reviewed by the patient advisory board. As part of the consent process, participants will be informed that the data they provide will not be actionable (in other words, it will not trigger a clinical investigation or intervention). Written informed consent will be obtained prior to performing any study assessments or procedures. Participants will be requested to consent to their medical records being made available to the study team throughout the study.

Participant Cohorts

ILD/IPF

The ILD/IPF cohort will include 20 participants recruited from the UCLH ILD service followed for 6 months. We will recruit patients across the spectrum of progressive to stable disease. We will analyze whether monitoring is able to detect progression earlier than the current standard (lung function test performed every 3 months or patient reporting to a clinician) and could help us identify progression earlier.

COPD

We will recruit 20 patients with COPD from our services in London and follow them for up to 6 months or until the first exacerbation, whichever is sooner. We will recruit patients with a history of exacerbations to increase the likelihood of identifying patients who would experience events during the study. We will analyze whether monitoring is able to detect exacerbations earlier than the current gold standard (patient reporting to a clinician) and therefore could be used to help patients get treatment earlier.

Posthospitalization COVID

For UCLH participants, we will define the population under study as people with a clinical diagnosis of COVID-19 (within 4-13 weeks of enrollment) and who report troublesome symptoms interfering with day-to-day activity present for more than 28 days following the onset of COVID-19 (n=20). A baseline assessment will be conducted remotely via a web-based questionnaire, which will obtain information on demographics, medical and psychiatric history, health behaviors, and medications. Participants will be asked about the symptoms, severity, and consequences (eg, hospitalization and ventilatory support) of their acute illness.

Consent

Informed consent will be sought at the end of the screening process and prior to the baseline clinical team meeting. Patients will have the study explained to them and will be given a copy of the participant information sheet (PIS). They will be given adequate time to consider taking part in the study and to ask any questions. Patients who are unable to give informed consent will not be recruited. Due to the nature of the remote monitoring study, we will optionally include a remote consent process for participants who are not able to attend the clinic in person. The remote consent process will be implemented using the REDCap electronic case report form (eCRF) e-Consent module to deliver the consent form; however, it is our preference to seek to keep wet signature/paper-based consent forms. These will be held both as electronic copies and hard copies.

Upon receipt of consent forms, participants will be booked for the enrollment training session. Prior to the session, participants will be provided a RALPMH study pack including study devices (Garmin, spirometer, and finger pulse oximeter) and equipment either by post or during a face-to-face session (via a cleanroom) if possible. Participants will receive a 45- to 60-minute training session on the use of the wearable devices, mobile sensors, and aRMT smartphone app. This will include a PIS leaflet summarizing key information and researcher contact details for future reference. The purposes of the study will be clearly explained, and participants will be provided with practical information, such as how to switch devices on and off, how to charge devices, and how to respond to questionnaires and digital tests on a notification via the app. Participants will receive a follow-up call 1 week after the start of data recording for any additional support as required. If participants do not have a suitable phone, we may provide one from a limited number of reserve devices. Precreated accounts for devices (eg, Garmin) will be registered using a study email address (eg, RALPMH022@domain.com) and dummy contact details. Baseline data will be collected in this first session via the study REDCap eCRF project instruments.

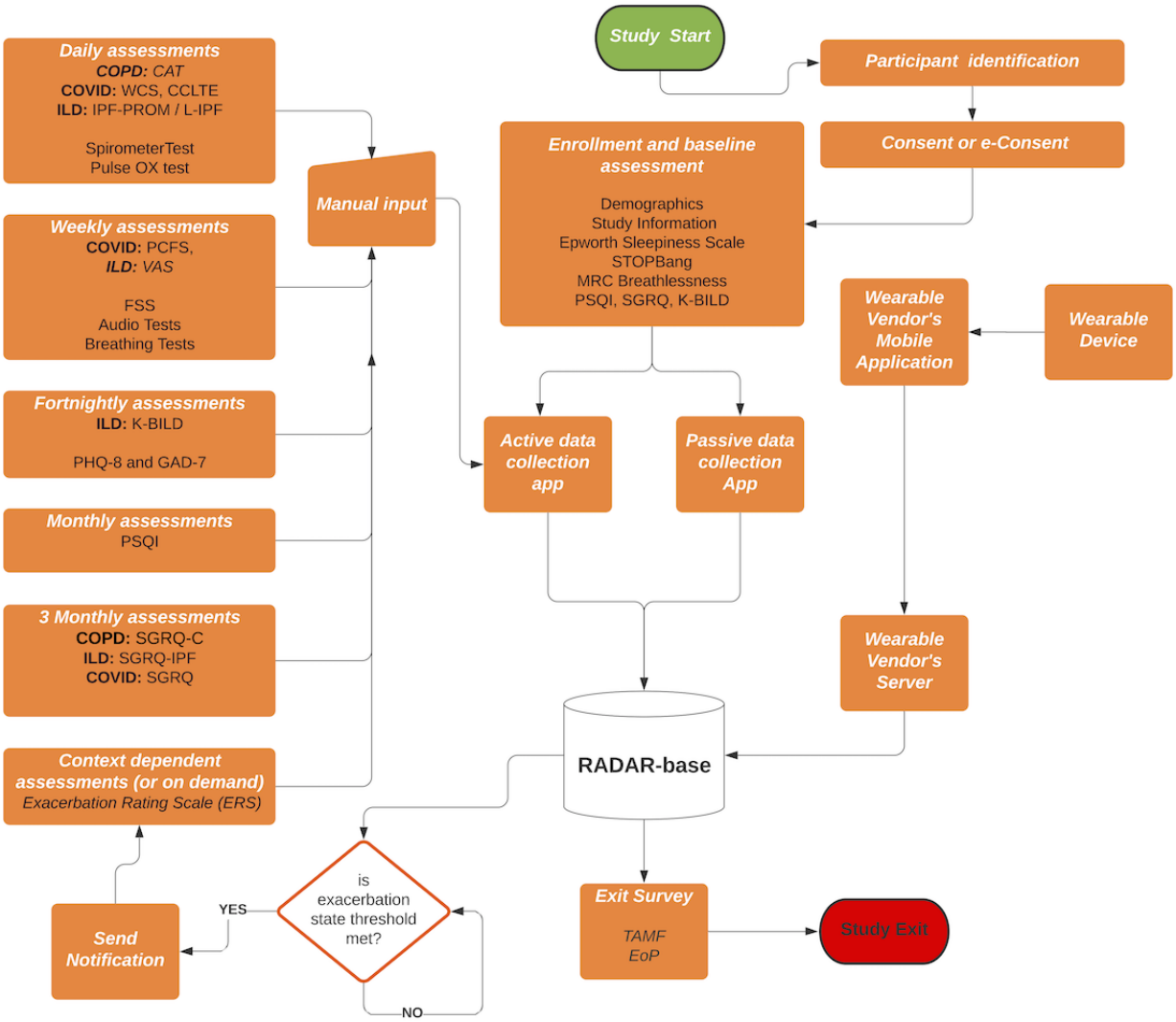
Results

Study Flow Chart

The study flowchart is shown in Figure 3. At the start of the study, participants remotely consent and are provided with the PIS. They are then provided a set of enrollment or baseline assessments to complete online.

All the scheduled active assessments (self-reports) that need manual input periodically are shown on the left, which are piped through the active data collection app to the RADAR-Base platform.

Figure 3. Study flow diagram. CAT: COPD assessment test; CCLTE: CDC COVID-19 long-term effects; COPD: chronic obstructive pulmonary disease; EoP: experience of participation; ERS: Exacerbation Rating Scale; FSS: Fatigue Severity Scale; GAD-7: Generalized Anxiety Disorder scale; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; l-IPF: living with idiopathic pulmonary fibrosis; KBILD: The King's Brief Interstitial Lung Disease; MRC: Medical Research Council; PCFS: post-COVID function status; PHQ-8: Patient Health Questionnaire depression scale; PROM: patient-reported outcome measure; PSQI: Pittsburgh Sleep Quality Index; RADAR: Remote Assessment of Disease and Relapse; SGRQ: St. George's Respiratory Questionnaire; TAMF: Technology Acceptance Model Fast Form; VAS: visual analog scale; WCS: World Health Organization COVID-19 symptoms.



The wearable device provided to participants connects to the wearable vendor's application, and the data are uploaded to the vendor's server, which is then synchronized to the RADAR-Base platform. On getting all the data, the RADAR-Base platform runs real-time data processing, and based on a threshold for exacerbation, it sends a notification and assessment for confirmation of the exacerbation in the form of the ERS. On exit or completion of the study, the participants will be asked about their experiences with the technology and the study.

Timeline

The timeline for the study is shown in Figure 4. The planning and technical support for the study were setup in March 2021. The recruitment and data collection phase has started in June 2021 and will end in June 2022 (1 year). At various points during this period, a review of the data quality and quantity will be performed. Data processing and analysis has started in July 2021 and is planned to end in October 2022. The publication writeup and final publication are planned from September 2021 to December 2022.

Figure 4. Study timeline. aRMT: Active Remote Monitoring Technology; eCRF: electronic case report form; RADAR: Remote Assessment of Disease and Relapse.

Progress to Date

The study started recruiting in the middle of June 2021. The data collection apparatus was setup and tested by clinical teams in April 24, 2021. All the questionnaires and their schedules are being served either via the RADAR active application or REDCap. Device selection (oximeter, spirometer, and wearable) was completed and the process of ordering devices was done before the start of recruitment. Garmin device (the choice of wearable in this study) integration has been completed, and the device has been tested with three dummy Garmin accounts for data sanity checks. All documentation required for the study was completed and was approved for funding and sponsorship. Patient and public involvement (PPI) feedback on the app and schedule was arranged with a demonstration of the app and protocol to participants. Relevant changes were incorporated based on PPI feedback. The ethics application was submitted and final approval was obtained prior to the start of recruitment. Eight participants have been recruited in the ILD arm of the study, and one participant has been recruited in the COPD arm. Looking at the data dashboard, it is evident that two exacerbations have already been captured. The real-time exacerbation detection system has been developed, and most of the parts of the infrastructure have been deployed and tested. The test data have been processed and are ready to feed into the algorithm. Currently, algorithm development is in progress, and we are using analyses from a priori data sets [13] and results from similar studies to inform the design of our algorithm.

Discussion

Conclusion

The RALPMH study was meticulously planned with collaboration from clinical teams, technical teams, and data analysis teams to provide a reference infrastructure for the use of wearable data for monitoring lung diseases. It specifically involves information regarding the feasibility and acceptability of remote monitoring and the potential of real-time remote data collection and analysis in the context of chronic lung disorders. Moreover, it provides a unique standpoint to look into the specifics of the novel coronavirus without burdensome interventions. It will help plan and inform decisions in future studies that make use of remote monitoring in the area of respiratory health.

Ethical and Regulatory Considerations

Assessment and Management of Risk

Details on risk assessment are provided in Table 4.

Table 4. Risk assessment.

Description of risk (indicate the level of likelihood: low/medium/high)	Risk priority (low, medium, high)	Risk owner	Proposed risk-mitigation measures
Data protection (eg, from intrusions)	Low	KCL[a]/SLAM[b]	Restrict access control to the data and use data sensitivity tiering. Encryption of data in transmission and at rest. Deidentification/pseudonymization once data are collected. Linked strong identifiers will be removed. Maintenance of software updates.
Threats to patient privacy	Low	KCL/SLAM	Data are handled with attention to deidentification and encryption. Higher risk data will typically be processed on edge devices with only aggregated data sent forward.
Patient fatigue with active or passive components of data collection	Medium	KCL/UCL[c]	Early engagement of acceptable burden levels to define expected tolerance levels. Opportunity to adapt the active data collection components in the course of the study.

[a]KCL: King's College London.

[b]SLAM: South London and Maudsley NHS Foundation Trust.

[c]UCL: University College London.

PPI

This project was developed following discussions with patients and their families, who wanted to ensure that their lung disease could be safely monitored at home. Patients from IPF and COPD groups read a draft protocol in full, and their feedback was used to improve the final submitted protocol. Information for patients and the public will be posted on the Breathing Matters website [45], and the final results will be shared with the patients.

Protocol Compliance

A repeating form on REDCap will be used to log any contact with participants and document any deviations from the protocol. Notifications to the principal investigator or sponsor will be reported appropriately.

Significant deviation from the protocol or noncompliance may result in the removal of the participant from the study upon review.

Logged telephone contact will be made with participants throughout the course of follow-up if there is a loss of data stream from a device. The participant will be contacted by telephone to ensure compliance and correct use. These contacts will be recorded as evidence of feasibility and acceptability outcomes. In addition to the telephone call provided after the introductory training session, participants will receive a further call after 1 month to address any further concerns or questions.

Access to the Final Study Data Set

The full data set for analysis will be limited to the immediate research groups and to members who must additionally hold current contracts with King's College London or University College London. The data analysis will be conducted in the appropriate data safe havens and university compute infrastructure.

A secondary pseudonymized (removing any potential identifiers, such as raw location and audio data, will be restricted to the locked primary data set), postprocessed, and deidentified set of derived features (eg, activity, HR, and sleep features) may be published for reference, benchmarking, and review as part of academic literature generated from this project.

Limitations

The size of the cohorts and the duration of the study might not be enough to get accurate and expected results, but this is typical for most pilot studies, as we intend to figure out the correct size and duration of the study required for expected results, which can be further used to plan future longitudinal studies. This can be partly mitigated by attempting to recruit people who are at high risk of exacerbation.

Dissemination Policy

Analysis and access to the primary data set will remain on secure King's College London/University College London infrastructure and will be jointly owned by the co-investigator groups and institutions. The secondary deidentified and pseudonymized data set may be published by the project partners as part of analysis and publication dissemination activity, and this may include the use of repositories, such as Synapse [46], with the intended time aim of 12 to 18 months after the conclusion of data collection. Partners may be notified of the published results on the project website [47].

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Authors' Contributions

AF: protocol development, platform operations, data analytics, and principal investigator; YR: protocol development, platform operations, data monitoring, and data analytics; JP: clinical expertise, protocol development, data analytics, and principal investigator; JH: clinical expertise, protocol development, data analytics, and principal investigator; MA: protocol development, research coordinator, clinical expertise, data monitoring, and data analytics; JJ: protocol development and clinical expertise; RD: protocol development; MO: protocol development.

Conflicts of Interest

JJ has received consultancy fees from Boehringer Ingelheim, Roche, GSK, and NHSX unrelated to the submitted work. YR, RJBD and AAF were actively involved in the development of RADAR-Base platform and applications. There were no financial interests for this work and contributions were made to open-source software. The other authors have no conflicts to declare.

Multimedia Appendix 1
Data analysis algorithms and models.
[DOCX File , 8 KB - resprot_v10i10e28873_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH Checklist (V 1.6.1).
[PDF File (Adobe PDF File), 626 KB - resprot_v10i10e28873_app2.pdf]

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Abbreviations

AE-IPF: acute exacerbations of idiopathic pulmonary fibrosis
aRMT: Active Remote Monitoring Technology
CCLTE: Centers for Disease Control and Prevention COVID-19 long-term effects
COPD: chronic obstructive pulmonary disease
eCRF: electronic case report form
ERS: Exacerbation Rating Scale
GAD-7: Generalized Anxiety Disorder scale
HR: heart rate
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
mHealth: mobile health
NHS: National Health Service
PCFS: post-COVID functional status
PHQ-8: Patient Health Questionnaire depression scale
PIS: participant information sheet
PPI: patient and public involvement
QoL: quality of life
RADAR: Remote Assessment of Disease and Relapse
RADAR-CNS: Remote Assessment of Disease and Relapse – Central Nervous System
RALPMH: Remote Assessment of Lung Disease and Impact on Physical and Mental Health
RFH: Royal Free Hospital
RHR: resting heart rate
SpO_2: oxygen saturation
UCLH: University College London Hospital
WHO: World Health Organization

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Protocol

Prevalence of SARS-CoV-2 Infection in Children by Antibody Detection in Saliva: Protocol for a Prospective Longitudinal Study (Coro-Buddy)

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Abstract

Background: The world has been confronted with the COVID-19 pandemic for more than one year. Severe disease is more often found among elderly people, whereas most young children and adolescents show mild symptoms or even remain asymptomatic, so that infection might be undiagnosed. Therefore, only limited epidemiological data on SARS-CoV-2 infection in children and young adults are available.

Objective: This study aims to determine the prevalence of SARS-CoV-2 antibodies in children from the city of Tübingen, Germany, and to measure the incidence of new cases over 12 months.

Methods: SARS-CoV-2 antibodies will be measured in saliva as a surrogate for a previous SARS-CoV-2 infection. Children will be sampled at their preschools, primary schools, and secondary schools at three time points: July 2020, October to December 2020, and April to July 2021. An adult cohort will be sampled at the same time points (ie, adult comparator group). The saliva-based SARS-CoV-2–antibody enzyme-linked immunosorbent assay will be validated using blood and saliva samples from adults with confirmed previous SARS-CoV-2 infections (ie, adult validation group).

Results: The first study participant was enrolled in July 2020, and recruitment and enrollment continued until July 2021. We have recruited and enrolled 1850 children, 560 adults for the comparator group, and 83 adults for the validation group. We have collected samples from the children and the adults for the comparator group at the three time points. We followed up with participants in the adult validation group every 2 months and, as of the writing of this paper, we were at time point 7. We will conduct data analysis after the data collection period.

Conclusions: Infection rates in children are commonly underreported due to a lack of polymerase chain reaction testing. This study will report on the prevalence of SARS-CoV-2 infections in infants, school children, and adolescents as well as the incidence change over 12 months in the city of Tübingen, Germany. The saliva sampling approach for SARS-CoV-2–antibody measurement allows for a unique, representative, population-based sample collection process.

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International Registered Report Identifier (IRRID): DERR1-10.2196/27739

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KEYWORDS

SARS-CoV-2; COVID-19; antibody; saliva; children; epidemiology

Introduction

The end of 2019 was marked by the emergence of a novel betacoronavirus, called SARS-CoV-2, which caused an outbreak in the Chinese city of Wuhan [1] and eventually spread to more than 180 countries. On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a global pandemic [2,3]. The novel virus spreads rapidly by efficient human-to-human airborne transmission [4]. Symptoms mainly include fever, cough, myalgia, loss of smell or taste, and a severe manifestation of pneumonia, but other symptoms of respiratory tract infections can also occur [5-7]. Children infected with SARS-CoV-2 typically experience mild disease or are asymptomatic [8]; few pediatric cases of severe or fatal COVID-19 have been reported [7]. In Germany, a total of 3,756,497 laboratory-confirmed SARS-CoV-2 infections, including 117,482 deaths, have been recorded as of July 2021 by the Robert Koch Institute in Berlin, Germany [9]. Among those, 225,270 were children under 10 years of age (6.0%) and 366,472 (9.8%) were adolescents aged 10 to 19 years [9]. At the time, the diagnostic strategy focused primarily on testing symptomatic individuals, and children may have been underrepresented in such records. Also, hospital-based studies or case series are biased toward recruitment of a selected group, and the fraction of identified children infected with SARS-CoV-2 is not generalizable to the larger population [10].

Epidemiologic surveys require an unbiased, sufficiently large, representative sampling approach. Screening for SARS-CoV-2–reactive antibodies allows for the retrospective identification of virus exposure and is amenable to large cohorts [11]. However, the prerequisite of blood sampling [12] is a hurdle to the screening of large pediatric cohorts, particularly outside of the medical context. Interestingly, antibodies are also secreted by mucosal tissues, and SARS-CoV-2–specific antibodies can be detected in saliva and other body fluids [13]. Saliva sampling as a noninvasive method (ie, it does not cause disturbance) for SARS-CoV-2 antibody measurements and is an elegant approach to rapidly assess the prevalence of SARS-CoV-2 infection in vulnerable cohorts at numbers appropriate for epidemiologic investigations [14]. Studies have reported the use of saliva not only for detection of respiratory viruses, including coronaviruses and SARS-CoV-2 [15], but also for detection of antibodies against measles, rubella, mumps, and hepatitis [16-18]. The number of seroprevalence studies benefiting from noninvasive saliva sampling is increasing [19].

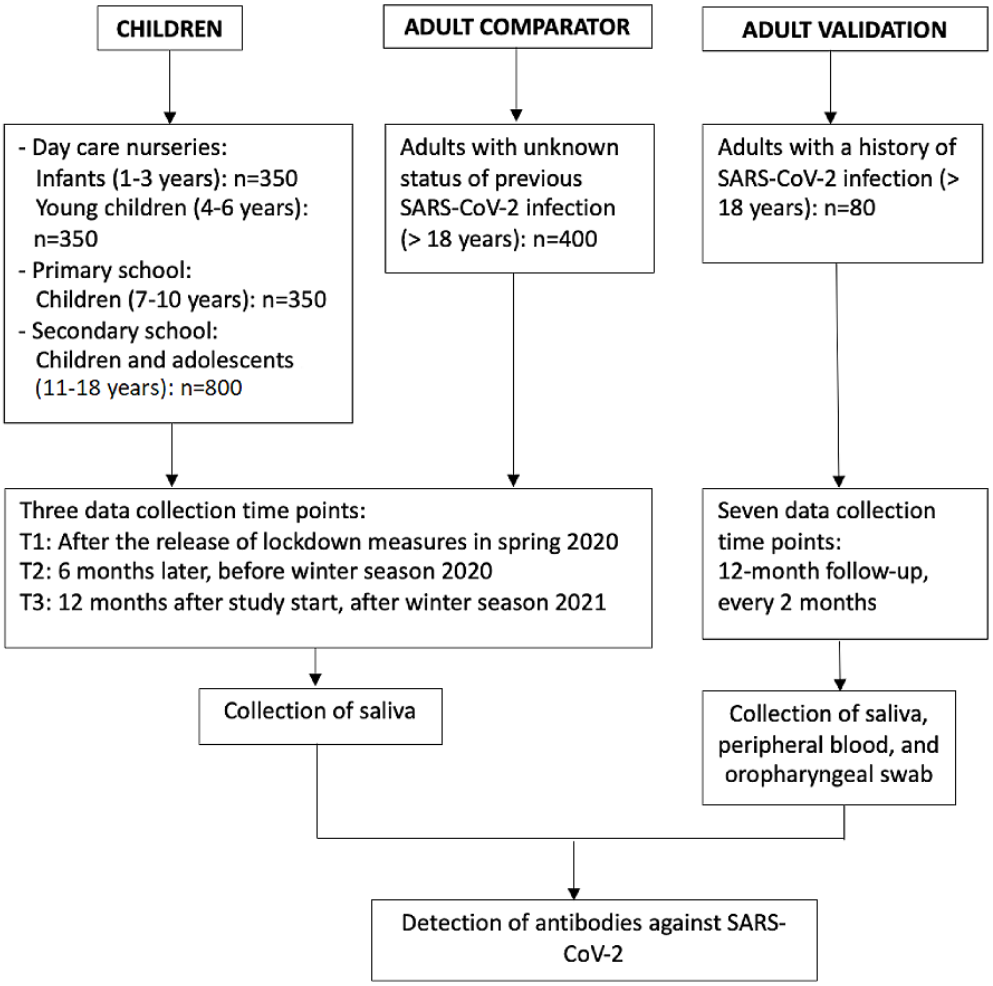
This study assesses the prevalence of SARS-CoV-2 antibodies as a surrogate for previous infections in children (aged 1-18 years) and measures the change of incidence over a 12-month period in a defined study area. The study takes place in Tübingen, a middle-sized university city in the Federal State Baden-Württemberg, Germany. Saliva samples from children were collected three times in preschools, primary schools, and secondary schools: summer 2020, 6 months later, and 12 months later (ie, before and after winter 2020-2021). SARS-CoV-2 antibodies will be measured in-house using a pre-established enzyme-linked immunosorbent assay (ELISA).

Methods

Study Design

Our study, titled Coro-Buddy (Coronavirus and Antibody Buddy), is a longitudinal, prospective, observational study to determine the prevalence of SARS-CoV-2 antibodies as a surrogate for previous infections in children and adolescents, and the change of antibody incidence over 12 months. Saliva samples from each study participant were collected at three time points: time point 1 (T1), after the release of lockdown measures in spring 2020 (ie, summer 2020); time point 2 (T2), before the winter season 2020; and time point 3 (T3), after the winter season 2021. An adult cohort (ie, adult comparator group) was sampled at the same time points to describe the seroepidemiological profile in adults. In addition, to establish and validate the SARS-CoV-2 antibody measurement process in saliva, an additional adult cohort group (ie, adult validation group) will have saliva and peripheral blood samples collected every 2 months at seven time points, over a 1-year follow-up. See Figure 1 for an overview of the study flow.

Figure 1. Study flowchart for participant sampling. T: time point.



Study Population

Children and adolescents were enrolled and sampled via preschools, primary schools, and secondary schools randomly spread over the Tübingen city area. In total, 1850 children and adolescents were enrolled: (1) preschools—infants aged 1 to 3 years (n=350) and young children aged 4 to 6 years (n=350), (1) primary schools—children aged 7 to 10 years (n=350), and (3) secondary schools—children and adolescents aged 11 to 18 years (n=800). Study participants and their families were informed about the study and its aims via their institutions. In addition to all relevant documents, families were also provided with a link to a video that explains the study (Multimedia Appendix 1) and procedures in an easy-to-understand way to ensure broad participation. Saliva was sampled after written informed consent has been given by parents or legal representatives. Assent from children aged 12 years and older was collected on the day of first sampling. Inclusion criteria include the following: aged 1 to 18 years, enrolled in an educational institution within the city of Tübingen, and written informed consent given or written assent given if the child is 12 years or older. Exclusion criteria include not attending a preschool or school in the city of Tübingen.

For the adult comparator group (n=400), any person aged 18 years and older living or working in Tübingen who had given written informed consent could be enrolled. For the adult validation group (n=40), the following individuals can participate in the study: those with a previous SARS-CoV-2 infection, confirmed by either quantitative polymerase chain reaction or by ELISA with a SARS-CoV-2–specific antibody at any time period before enrollment, who have given written informed consent. Blood and saliva samples are being collected every 2 months for 12 months (Figure 1).

Sample Size

Tübingen has a total of 91,656 inhabitants; among them, 4910 are children under the age of 6 years and 8366 are children between the ages of 6 and 18 years (≤6 years: n=4061; 7-18 years: n=6621, as of December 31, 2019). Therefore, in total, 13,276 children were living in Tübingen at the time of the study; of these, we aimed to recruit 1850 children and young adults. In addition, 400 adults will be included as an adult comparator group. At the time of planning, 567 out of 100,000 inhabitants—as determined by the Robert Koch Institute in Berlin, Germany, on June 1, 2020—have had a confirmed SARS-CoV-2 infection in the county of Tübingen, but the number of unreported and asymptomatic infections is believed

to be higher. Therefore, we expect to have at least 2.2 positive cases in the adult group; in the event that children are infected at an equal frequency, we expect to find at least 10.4 positive cases in children at T1.

Questionnaire

A structured questionnaire with six questions addressing exposure to SARS-CoV-2 infection in the family was administered at each of the three time points to the parents and representatives of the children as well as to the participants in the adult comparator group (Multimedia Appendix 2).

Saliva and Blood Collection

Saliva samples were collected from children 6 years and below using an ORACOL S14 saliva collection device (Malvern Medical Developments) by gently brushing the gumline for 2 minutes. For children 7 years and above, 3 mL of saliva was collected by spitting into a plastic tube; 30-mL multipurpose containers (item No. 201150; Greiner Bio-One) were used for this purpose. Saliva samples were kept on ice for a maximum of 3 hours before further processing. The ORACOL S14 saliva collection device was centrifuged at 2500 rpm for 10 minutes and the 30-mL multipurpose containers were centrifuged for 6 minutes. Supernatant was transferred into a 2-mL microtube and inactivated using a solvent and detergent treatment to a final concentration of 0.3% tri-*n*-butyl phosphate and 1% Triton X-100. Samples were immediately stored at –20 °C. Blood was collected by vein puncture into 9-mL lithium-heparin Monovettes; the plasma was obtained by centrifugation at 1400 rpm for 10 minutes and stored at –20 °C.

Laboratory Analysis

Saliva and blood samples were processed according to standard procedures and stored at –20 °C until analysis by ELISA to identify SARS-CoV-2–reactive antibodies. A previously established and validated in-house ELISA to detect antibodies against SARS-CoV-2 in saliva was performed [20]. Blood samples from the validation group cohort will be analyzed using a certified commercial ELISA by EUROIMMUN to quantify immunoglobulin G reactive to the S1 domain of the of SARS-CoV-2 spike protein.

Data Management

The case report form is the source document for all personal data. Each participant included in the study received a unique identifier. All data were collected on paper forms and were entered and pseudonymized into an electronic database.

Data Analyses

Data will be typed into Excel (version 16.51; Microsoft), and graphics will be generated with Prism (version 9.1; GraphPad) and RStudio (version 1.2.5001) running R (version 4.0.4; The R Foundation). Simple descriptive statistical analyses will be conducted. Depending on the classification of the data, parametric or nonparametric tests will be used. Correlation and regression models will be analyzed using RStudio. The estimated prevalence will be computed and adjusted using the R package epiR (version 0.9-43).

Ethics Approval and Consent to Participate

This study was conducted with the approval from, and consent form signed by, the parents and participants, according to the protocol that was reviewed and accepted by the Ethics Committee of the University Hospital Tübingen on June 24, 2020 (reference No. 20-231/BO1). Each study participant was protected against invasion of privacy. Written informed consent was obtained from the participants, with parental consent and participant assent from those 12 years of age and older. The trial was retrospectively registered at ClinicalTrials.gov (NCT04581889) on October 10, 2020.

Data Availability Statement

Data will be available upon the study's completion.

Results

The first study participant was enrolled in July 2020, and recruitment and enrollment continued until July 2021. We have recruited and enrolled 1850 children, 560 adults for the comparator group, and 83 adults for the validation group. We have collected samples from the children and the adults for the comparator group at the three time points (T1-T3). We followed up with participants in the adult validation group every 2 months and, as of the writing of this paper, we were at time point 7. We will conduct data analysis after the data collection period.

An amendment to the protocol was submitted to, and approved by, the Ethics Committee of the Tübingen University Hospital for blood collection from antibody-positive children during data collection at T3. This study is expected to conclude in November 2021.

Discussion

The world was confronted with the COVID-19 pandemic, which has become the biggest public health crisis of recent times, has caused a large number of deaths, and has become a burden on intensive care facilities [2]. The majority of affected persons are older than 18 years, although adolescents and children can also become infected, with recent estimates in the range of 5% [21-23]. Different study designs can provide information on the transmission dynamics in children. Large population-wide serosurveillance studies have been performed in Europe using blood samples [11,24,25]; however, in order to facilitate large population studies in school-aged children, especially if multiple samples are collected from within the same population, saliva samples should be considered. With these factors in mind, the Coro-Buddy study was developed as a prospective, longitudinal study and will report the prevalence of SARS-CoV-2 infection in children in a sample that is representative of the study area, Tübingen, a university city in the south of Germany. The study will also be able to report on the prevalence of previous SARS-CoV-2 exposure in the different age cohorts—1 to 6 years, 7 to 10 years, and 11 to 18 years—as well as the incidence of new cases at three different time points, representing the end of school closures in Germany in summer 2020, and before and after the winter 2020-2021 period.

Children were enrolled and sampled at their respective preschools or school centers to ensure representativeness of the young population in the study area. The infection rate will be determined by measuring antibodies against SARS-CoV-2 in saliva via noninvasive sampling. This approach is particularly amenable for community studies where the significance of the outcome increases by unbiased sampling. The study will also report on a validated saliva-based SARS-CoV-2–antibody ELISA procedure that can be used in future antibody prevalence studies. In addition, the study will report on the number of SARS-CoV-2 infections per institution; this data could contribute to comparative analysis with data collected beyond this study to better understand the pandemic retrospectively.

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Authors' Contributions

YTP drafted the manuscript and is coordinating and conducting the study. EF, JMG, and LB drafted the manuscript and are conducting the study. AK, JH, and RF conceptualized and designed the study, wrote the study protocol, and revised the manuscript. RF, CH, and KE designed and are conducting the antibody assays.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Coro-Buddy (Coronavirus and Antibody Buddy) study video.
[MP4 File (MP4 Video), 26425 KB - resprot_v10i10e27739_app1.mp4]

Multimedia Appendix 2
Study questionnaire.
[PDF File (Adobe PDF File), 245 KB - resprot_v10i10e27739_app2.pdf]

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Abbreviations

Coro-Buddy: Coronavirus and Antibody Buddy
ELISA: enzyme-linked immunosorbent assay
T1: time point 1
T2: time point 2
T3: time point 3

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Protocol

Improving the Follow-up Rate for Pediatric Patients (0-16 years) of an Eye Hospital in Nepal: Protocol for a Public Health Intervention Study

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Abstract

Background: The follow-up of pediatric patients ensures regular ocular morbidity monitoring and better treatment outcome. Hiralal Santudevi Pradhan Institute of Ophthalmic Science (Bharatpur Eye Hospital [BEH]) noticed that the follow-up rate was only 22% among its pediatric patients. Several factors like lack of awareness and forgetfulness among patients may contribute to a lower number of follow-up visits. Therefore, BEH decided to find if counseling and reminders through SMS text messaging and phone calls would improve the follow-up rates.

Objective: This study aims to evaluate the impact of interventions like counseling and reminder SMS text messaging and phone calls in improving the follow-up rate of pediatric patients.

Methods: This is a public health intervention study being conducted using quantitative analysis. All children (0-16 years) with ocular conditions requiring at least 3 follow-up visits in the study period will be included. In all, 264 participants will be allocated to 3 groups: routine standard care, counseling, and reminders with SMS text messaging and phone calls. In counseling, patients will take part in 20-minute counseling sessions with trained counselors at each visit, and information leaflets will be provided to them. In the reminder SMS text messaging and phone call group, patients will receive an SMS text message 3 days prior and a phone call 1 day prior to their scheduled visits. Patients attending within 2 days of the scheduled date will be considered compliant to follow-up. The proportion of patients completing all the follow-up visits in each group will be assessed. Informed consent will be taken from parents and children. Univariate and multivariate analyses will be conducted.

Results: The ethical approval for this study has been obtained from the Ethical Review Board (ERB) of Nepal Health Research Council (ERB protocol registration #761/2020 P). The data collection was initiated on January, 24, 2021, but due to the COVID-19 pandemic, as of September 2021, we have only been able to enroll 154 of the planned 264 participants (58.3% of the sample size).

Conclusions: This study will reliably document not only the factors associated with follow-up rate through an intervention package (counseling and reminders through SMS text messaging and phone calls) but also the cost effectiveness of the intervention package, which can be applied in all the departments of the hospital.

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KEYWORDS

counseling; follow-up; intervention study; pediatric patients; ophthalmology; public health; Nepal

Introduction

Childhood visual impairment and blindness remains an important public health issue. It is estimated that around 14 million children in the world are blind [1]. The Nepal Pediatric Ocular Disease study found that the prevalence of blindness and visual impairment in the community was 0.068% (95% CI 0.02-0.12) and 0.097% (95% CI 0.04-0.15), respectively [2]. Increasing the global knowledge base for planning for childhood eye care services is a top priority in order for children with visual impairment to realize their full visual potential [3]. Follow-up of pediatric patients is important for their regular ocular morbidity monitoring, especially for amblyopia management [4]. Bharatpur Eye Hospital (BEH) observed that there was poor adherence to follow-up visits. An exploratory observation of data of the first week (January 1, 2010, to January 7, 2019) revealed that the follow-up compliance was very low among children aged 0 to 16 years in the pediatric department. Among the children advised for follow-up, only 22% were found to have come for at least 1 follow-up visit. A problem analysis showed that a lack of awareness in children and their parents regarding the importance of follow-up and patients forgetting dates of the follow-up visit (usually when there is long gap for follow-up) may be the major contributing factors for poor adherence to follow-up.

A study from India revealed that distance and cost were major barriers, as was the inability of the eye care center to communicate the importance of follow-up [5]. Another study done in Nepal found poor follow-up rates for patients following cataract surgery, which, however, improved after implementation of a high-quality pediatric counseling service, follow-up program, tracking system, and cell phone reminders [6]. Many studies have compared different methods of reminder options like telephone calls, email, and SMS text messaging in order to improve the compliance to follow-up [7-10]. Hence, a public health intervention study has been planned to estimate the effect of intervention package (counseling and reminder SMS texts and phone calls) for improving the follow-up rates in pediatric patients.

The primary objectives are to determine if parental counseling has an impact on adherence to follow-up and to determine if reminders through phone calls and SMS texts increase the follow-up rate in pediatric patients. The secondary objective is to assess the cost-effectiveness of counseling and reminder SMS texts and phone calls. We hypothesize that counseling will increase the follow-up rate from 22% to 50% and reminders through phone calls and SMS texts will increase the follow-up rate from 22% to 25% at the site of the study (mentioned in the next section).

Methods

Study Design and Setting

This public health intervention study will be conducted at Hiralal Santudevi Pradhan Institute of Ophthalmic Sciences which includes 13 satellite clinics and 1 base hospital (Bharatpur Eye Hospital [BEH]). The study participants will be enrolled only from the pediatric department of BEH, a centrally located tertiary eye hospital in the Chitwan district of Nepal. All pediatric patients 0 to 16 years of age meeting the inclusion criteria will form the study population. In the pediatric department of BEH, children aged 0 to 16 years are being examined as per the hospital policy.

The inclusion criteria are all pediatric patients 0 to 16 years of age advised for at least 3 follow-up visits within a 6-month period at BEH, parents or guardians of children who own a mobile phone or have daily access to a phone and are able to use the SMS text feature on these phones, and parents willing to enroll their children in the study.

The exclusion criteria are children who require fewer than 3 follow-up visits, children with ocular conditions requiring daily follow-up visits (because it is not feasible to send the reminder phone call and SMS text for daily follow-up), children who have already been treated and are under regular follow-up, children with ocular conditions requiring follow-up beyond 6 months, parents or guardians of the children who are not willing to participate in the study, and those who have been called but do not answer after 3 attempts

Sample Size

Bonferroni correction (level of significance P=.05; k=3 comparisons) was adopted for sample size calculation with consideration to the proportion of attendance in counseling (p1) and reminder SMS texts and phone calls (p2) as 50% (0.5) and 25% (0.25), respectively. An estimated sample size of 264 pediatric patients will be targeted with an adjusted significance level of .02, 80% power, and 10% loss to follow-up.

Intervention Package

Counseling Group

In this group, after the children have been examined, a treatment plan and follow-up schedule will be advised by the pediatric ophthalmologist to the parents or guardians along with the child. The parent or guardian and the child will receive counseling from a trained counselor (SK) as per the set counseling protocol in every follow-up visit where the disease-specific leaflet will be used as a counseling tool, a copy of which will also be handed over to them. A counseling protocol for the common ocular conditions has been designed by the research team. The counselor will be oriented and trained as per the counseling

protocol a week before the participants are enrolled in the study. Children, along with their parent or guardian, will be receiving counseling irrespective of patient age, parental education, ocular conditions, and other factors. If more than one guardian or both mother and father are accompanying the child, both will be included in the counseling session. The counselor will deliver verbal counseling for all participants in all follow-up visits irrespective of the ocular conditions and other factors. The counseling session for all participants will last for 20 minutes.

SMS Text and Phone Call Reminder Group

In this group, after the children have been examined and a treatment plan and the follow-up have schedule been advised, they will be discharged from the department. They will receive an SMS text 3 days prior to and a phone call 1 day prior to their scheduled follow-up visits. Text messages will be sent until it is confirmed that the sent message has been received. In the case of message delivery failure, it will be sent again 3 more times to ensure successful delivery. If the SMS text is not delivered after 3 attempts, then a message will be sent to the next phone number (if available) as recorded in the proforma during the interview. A phone call will be deemed to be completed once it is received by the respondent; calls will be repeated at least 3 times if the phone is not answered in the first instance. If the call is not answered even after 3 attempts, the participant will be excluded from the study.

The assistant (DA) will be responsible for making the reminder SMS and calls, making the records, and tracking the follow-up patients. The standard text and the call format have been developed in the local language (Nepali).

Routine Standard Care Group/Control Group

In this group, the children will undergo visual acuity testing and refraction by an optometrist. The pediatric ophthalmologist will perform detailed ocular examination and advise necessary investigations to diagnose and formulate a treatment plan. Basic counseling will be done by the consultant regarding the ocular condition, treatment, and need for follow-up. No additional counseling or reminders will be performed for these patients. They will be discharged from the department and advised for follow-up as per the hospital protocol. The follow-up schedule as per the hospital protocol for common ocular conditions is shown in Table 1.

Table 1. Schedule for follow-up for different ocular conditions.

Ocular condition	Recommended guidelines for follow-up [11]
Congenital naso-lacrimal duct obstruction	Once every 4 weeks
Keratitis	Depending on severity, at least once a week
Allergic conjunctivitis	Once every 2 weeks
Ocular injury	Depends on severity of injury, daily to once a week
Pediatric cataract	Once every 2 weeks
Strabismus	Once every 2 weeks
Amblyopia	Once every 4 weeks
Retinopathy of prematurity	Once every 2 weeks

Outcomes

The primary outcome is the proportion of children completing all 3 follow-up visits in the routine standard care group, counseling group, and reminders through SMS texts and phone call group.

The secondary outcomes include the effect of parental or guardian education status in compliance to follow-up, the visual status of the children in subsequent follow-up visits, the effect of traveling distance and cost in compliance to follow-up, and the cost-effectiveness of the intervention.

Independent Variables

The independent variables will include the following sociodemographic factors: gender, age, ethnicity, educational status, occupation of parent or guardian, attendant relationship with the child (of parent or guardian attending with the child), distance traveled, and cost for the travel to the hospital.

Study Procedure

All participants will be enrolled in the study after fulfilling the inclusion criteria and administering informed consent. Recruitment will be conducted over a 6-month period. Participants will be assigned a unique code which will be a 6-digit number generated by using the last 3 digits of the patient's medical record number and the last 3 digits of the parent's or guardian's mobile phone number. The participants will be entered into 3 groups, such that the first patient will be enrolled to the routine standard care group, the second to the counseling group, and the third to the group of SMS texts and phone call reminders. The same sequence will be followed for every participant until the required sample size has been attained. Before the actual start of the recruitment, 2 dry runs were conducted to understand the flow of the patients and logistics of the study.

After registration, the patient will be guided by the Outpatient Department (OPD) facilitator to the vision and refraction room and then to the consultant room. After ocular examination, treatment and follow-up advice, the consultant will paste a colored sticker on the patient's file to indicate the potential study participant. There will be a separate and dedicated place for the pediatric ophthalmologist, assistant, and the counselor (Multimedia Appendix 1).

Patients with a colored sticker on their OPD file will be referred to the assistant room. The assistant will take the written consent from the children in an assent form (if 9 years or older) and from their parents or guardians in a consent form after explaining the study and group and selection to them (Multimedia Appendix 2 and 3).

A unique number will be allotted to the patient (generated through the medical record number and mobile phone number of the patient). The unique ID of the participants will be recorded in the proforma and on the examination file by the assistant. He will fill all the details in the proforma (Multimedia Appendix 4) and also enter the details in a Microsoft Excel sheet.

The patients assigned to counseling will be sent to the counselor. The counselor will conduct a counseling session based on the ocular condition and follow-up plan. Counseling will be done as per the prescribed counseling protocol. After counseling, the counselor will provide the information leaflets, and the patient will be asked to visit the optical dispenser or pharmacist.

For patients assigned to the SMS text and phone call reminders or control groups, the necessary details will be filled in the proforma and Excel sheet before they are discharged by the assistant.

Identifying the Follow-up Patients

The study participants will have a colored sticker attached to their OPD card during their first visit. The assistant will provide a unique code to the study participants, which will be written on top of the colored sticker attached on their OPD card. Thus, during the follow-up visit, the participants will be easily identified by this colored sticker with the unique code in their OPD card. The assistant will match the unique code of the patient with the computer records and find out the study group of the patients in each follow-up visit.

In case the patient card is lost or if the patients comes with a new OPD card during follow-up, the earlier registered medical record number will not match with the new medical record number. In this case, the patient's identity will be confirmed by matching the patient's name, gender, age, guardian's name, and guardian's phone number.

Compliance to Follow-up

The participants' first visit to the hospital and the scheduled 3 follow-up visits need to be completed for them to be considered compliant to the follow-up. Only those participants who complete the first follow-up will be considered for second follow-up, and only those coming for second follow-up will be considered for third follow-up [6]. The patient will be considered compliant to follow-up if he or she comes within the window period of 2 days. The rescheduling of the next follow-up date will be calculated from the attended date as per the follow-up schedule for each ocular condition.

The purpose of observing compliance to follow-up is to determine the impact of counseling and reminders through SMS texts and phones call for the increment of the proportion of children completing their 3 follow-up visits based on the developed proforma and to find out the significant proportion in the follow-up rate between the 3 different groups.

Record Maintenance

Records of the participants from the first visit to all the follow-up visits will be maintained in the department by the assistant. The details will be entered for each participant as per the proforma. If both parents accompany the child, only the mother's detail will be included. However, when both parents accompany the child but only the father has access to a mobile phone, his details will be recorded.

The record of the patients will be kept even if they come for follow-up beyond the set window period (2 days); however, in this case, they will not be considered compliant to follow-up.

The assistant will also assign the patients to a group (regardless of whether they receive an intervention) as per the study procedure. A follow-up recording file (3 in number, 1 each for routine standard care, counseling, and reminders through SMS texts and phone calls) will be maintained. These follow-up details will also be entered in the Excel sheet on the same day as a backup in case the paper records are lost or destroyed. The entry of all the details from the proforma will be entered and stored in an Excel sheet by the assistant. The status of record maintenance will be regularly monitored by the ophthalmic officer (BP). The assistant will also be responsible for tracking the follow-up visits and updating the schedule for executing the reminder SMS texts and phone calls (Multimedia Appendix 5).

Data Collection and Management

In order to obtain the required data from the participants, a proforma has been designed based on variables pertaining to sociodemographics and follow-up. The proforma has been developed in the English language, and the sequence of questions will be carefully looked into. Questions are arranged in the following manner: the first pertain to identification, are followed by those pertaining to sociodemographic information, and are concluded by questions pertaining to follow-up points.

Training of the Team

All team members will receive training on the study process. The principal investigator (MS) or coprincipal investigator (GB) will brief the team on the process during the training session, including on the consent of the participant, being polite and considerate, the standardized delivery of questions, and the noting of the responses. During the training sessions, each and every question will be explained to the team, and queries will be addressed.

Data Editing

Data will be submitted as early as possible to the investigator team so that they can edit the proformas and make them ready for data entry.

Data Entry and Validation

The data entry program will be designed in Excel. The study optometrist and coprincipal investigator will do the data entries. Corrections will be made where required by the study's ophthalmic officer, who will compare the computer data file with the original proforma.

Data Monitoring and Confidentiality

The data monitoring will be performed by an internal monitoring committee on a weekly basis. All the information collected will be stored only with the investigators. The publications will not reveal any private information of any of the participants.

Data Analysis

Data will be processed and analyzed using Excel (Microsoft) or Epi Info (Centers for Disease Control and Prevention).

Univariate Analysis

Univariate logistic regression analysis will be conducted by comparing 2 variables for each variable of interest using odds ratios (ORs) and their 95% CIs. The likelihood ratio test will be used to estimate ORs and 95% CIs for all associations of interest.

Multivariate Analysis

Multivariate logistic regression analysis will be performed to adjust for the simultaneous effects of multiple factors on the outcome variable. The criteria for inclusion of factors in the multivariate analysis are to include all variables from the univariate analysis with a *P* value of .1 along with all the variables of known importance. To assess the importance of each variable included in the model, the Wald statistic for each variable will be used.

Before the multivariate analysis is conducted, the association among independent variables will be checked by a chi-square test. For independent variables having more than 2 categories, dummy variables will be created. All the variables meeting the above selection criteria will be entered one by one, starting with the highly significant factors from the univariate analysis. The overall significance of independent variables in the model will be assessed by likelihood ratio test (G statistic). Selection of the final model will be based on parsimony, biological interpretability, and statistical significance. The parameters of the logistic regression model will be estimated by the maximum likelihood method. The adjusted ORs and their 95% CIs will be computed using the estimates of parameters of the final model. The dependent variable will be dichotomous: either compliance with the follow-up instruction has increased, or it has remained changed (no difference) from before the intervention study to after it. The final model will be tested for goodness of fit by Hosmer- Lemeshow chi-square (X^2) statistic. *P* values will be noted to assess the model fit. Imputation and intention to treat analysis will also be conducted (if required).

Cost-Effectiveness Analysis of Counseling and Reminder SMS Texts and Phone Calls

The total costs involved in implementing the interventions will be compared with the attendance of follow-up patients and the revenue generated through their follow-up sessions. The intervention costs include the salary for the team members. In addition to the costs for the phone calls and reminder SMS telecommunication charges, the cost for equipment, stationery, and the charges for utility services like water and electricity will also be included as the cost for implementing interventions. Cost effectiveness will be analyzed separately for counseling and reminders (phone calls and SMS texts) by calculating the total cost incurred per attendance of follow-up in each intervention group and the total revenue generated through the fee for the OPD ticket, investigations, medicines, and glasses provided during the follow-up visits.

Ethical Approval

The ethical approval has been obtained from Ethical Review Board (ERB) of the Nepal Health Research Council (ERB protocol registration #761/2020 P). The data collection was initiated on January 24, 2021, but due to the COVID-19 pandemic, as of September 2021, we have only been able to enroll 154 of the 264 participants (58.3% of the sample size).

Results

Descriptive statistics will be presented, and demographic variables will be summarized by computing means with SD for continuous variables and proportions for categorical variables. Associations between sociodemographic variables and compliance rates will be presented. The associations will be computed using categorical variables. Two dry runs were conducted to assess the logistics and flow of participants. The first dry run was conducted by taking only 10 patients who were not the actual study participants, but the second dry run was conducted with the actual participants as per the inclusion and exclusion criteria. A total of 38 study participants were enrolled for a duration of 1 month for the second dry run. Of these participants 13, 13, and 12 were divided into the standard care group, counseling group, and reminder with SMS texts and phone call groups, respectively. The mean age of the children was 3.71 (SD 0.61) years, with a range of 0.07 to 14 years. There were more male children 24 (63.16%) as compared to female children 14 (36.84%). Most of the children were of Aryan descent (63%), and more than 80% of the children were accompanied by their mother. Only 7 out of the 38 patients attended the follow-up visit. All those who attended have attended only the first follow-up visit. Three participants were from reminder group, two were from the counseling group, and two were from the standard care group. Out of the 38 children, 14 (36.8%) were diagnosed with congenital naso-lacrimal duct obstruction and 7 with amblyopia, with the others having conjunctivitis, eye injury, corneal ulcer, or squint.

Discussion

This study will reliably document not only the factors associated with follow-up rate through an intervention package (counseling and reminders through SMS texts and phone calls) but also the cost effectiveness of the intervention package. Compliance to follow-up visits is important for better outcomes of treatment for any condition. It is equally important for children with visual problems to comply with the follow-up so that they can receive complete treatment and be prevented from going permanently blind in some cases. Different studies have shown varied results regarding the effect of these interventions. Follow-up rates have found to be improved with these types of intervention in some studies while other studies show no significant improvement with the interventions [12-17]. One intervention may work better than others in some studies. We are testing these interventions

to improve the follow-up rate of pediatric patients with ocular problems. Loss or noncompliance with the scheduled follow-up visits by patients who have been advised to come for follow-up is a major issue in many areas of clinical practice. Noncompliance has been a major problem with pediatric patients undergoing treatment at the Pediatric Ophthalmology Department at BEH, where only 22% of those advised attended the follow-up. Therefore, this study is attempting to determine which intervention strategy would work better for this problem. Any intervention found effective will be applied to other departments and will be implemented as the hospital policy in the future.

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Authors' Contributions

MS, GB, SKR, AGG, BP, RG, DSC, and RB conceptualized and designed the study. DA and SK were responsible for the consent form and information leaflets. SK provided counseling to the study participants. MS, GB, and SKR drafted the protocol manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient flowchart.
[DOCX File , 42 KB - resprot_v10i10e31578_app1.docx]

Multimedia Appendix 2
Assent to participate in the study.
[DOCX File , 13 KB - resprot_v10i10e31578_app2.docx]

Multimedia Appendix 3
Consent to participate in the study.
[DOCX File , 13 KB - resprot_v10i10e31578_app3.docx]

Multimedia Appendix 4
Proforma for the ocular condition.
[DOCX File , 33 KB - resprot_v10i10e31578_app4.docx]

Multimedia Appendix 5
Format of SMS texts and phone calls.
[DOCX File , 12 KB - resprot_v10i10e31578_app5.docx]

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Abbreviations

BEH: Bharatpur Eye Hospital
ERB: Ethical Review Board
OPD: Outpatient Department

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Protocol

Technology-Supported Guidance Model to Support the Development of Critical Thinking Among Undergraduate Nursing Students in Clinical Practice: Protocol of an Exploratory, Flexible Mixed Methods Feasibility Study

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Abstract

Background: Critical thinking is an essential set of skills in nursing education, and nursing education therefore needs a sharper focus on effective ways to support the development of these skills, especially through the implementation of technological tools in nursing education.

Objective: The aim of this study protocol is to assess the feasibility of a technology-supported guidance model grounded in the metacognition theory for nursing students in clinical practice.

Methods: Both quantitative (research questionnaires) and qualitative (focus group interviews) approaches will be used to collect data for a feasibility study with an exploratory, flexible mixed methods design to test a newly developed intervention in clinical practice.

Results: The intervention development was completed in December 2020. The intervention will be tested in 3 independent nursing homes in Norway.

Conclusions: By determining the feasibility of a technology-supported guidance model for nursing students in clinical practice, the results will provide information on the acceptability of the intervention and the suitability of the outcome measures and data collection strategy. They will also identify the causes of dropout and obstacles to retention and adherence.

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KEYWORDS

critical thinking; guidance model; feasibility; technology; medical education; nursing education; clinical practice

Introduction

Background

Critical thinking is an important outcome of nursing education [1], and clinical practice is essential for its development [2]. In clinical practice, a nurse preceptor serves as a tutor or mentor to guide nursing students toward the acquisition of necessary skills [3].

Nursing students may experience challenges and difficulties in their clinical practicum, such as not knowing who the main nurse preceptor responsible for guidance is, receiving limited guidance, experiencing a change of nurse preceptor, or having a poor relationship with the nurse preceptor [4]. Likewise, nurse

preceptors may lack the resources, experience, and training in guiding nursing students [5-7]. These challenges in guiding nursing students in clinical practice may negatively influence their development of critical thinking [8].

The introduction of technological tools in nursing education has opened new possibilities for addressing these challenges and improving outcomes related to critical thinking [9], but only a few studies have examined the effectiveness of technological tools in supporting the development of critical thinking skills in nursing students. Strandell-Laine developed a technological intervention to improve cooperation between nursing students and nurse educators to improve self-efficacy and nursing competence; the intervention was not significantly effective in improving individual outcomes, but it strengthened communication between students and nurse educators [10]. Mettiäinen developed a technology-based app for feedback and assessment in the clinical guidance of nursing students [11]. In a pilot study, Mettiäinen et al [11] found that nursing students had positive attitudes toward the use of technological tools (eg, apps) during their guidance in clinical practice, and she concluded that such apps are a viable option for the guidance of nursing students in clinical practice.

Owing to the importance of critical thinking in nursing education, interventions that support critical thinking and its development are needed. This study provides a protocol for a feasibility study, which is one stage of a complex intervention [12]. The feasibility study is a part of the main study, *Technology-Supported Guidance to Increase Flexibility, Quality, and Efficiency in the Clinical Practicum of Nursing Education*, conducted at Lovisenberg Diaconal University College (LDUC), Oslo, Norway. The main study included a mixed methods systematic review, feasibility study, randomized controlled trial (RCT), and follow-up study. Protocols for the systematic review of mixed methods [13] and RCTs [14] have already been published.

Study Aim

The overall aim of this study is to explore the feasibility of a technology-supported guidance model for nursing students in clinical practice.

Objectives

The purpose of this study is to assess the feasibility and acceptability of a newly developed technology-supported guidance model in clinical practice among nursing students, nurse preceptors, and nurse educators; assess the feasibility and suitability of the primary and secondary outcome measures; assess the recruitment strategy; assess the data collection strategy; and identify potential causes of dropout and hindrances to participant recruitment, retention, intervention fidelity, and adherence to the intervention.

Research Questions

How feasible and acceptable is the newly developed technology-supported guidance model and the overall intervention among nursing students, nurse preceptors, and nurse educators? Are the outcome measures feasible and suitable for an RCT? How feasible is the chosen data collection strategy? How suitable is the participant recruitment strategy? What causes dropout and what hindrances can occur in relation to recruitment, retention, intervention fidelity, and adherence? How can these hindrances be minimized?

Methods

Overview

According to Giangregorio and Thabane [15], there is no universal agreement on the definitions of feasibility and pilot studies. Some definitions may overlap, whereas others distinctively differ in their understanding of feasibility and pilot studies. The Medical Research Council Framework for Complex Interventions does not make a clear distinction [16], whereas the National Institute of Health Research in the United Kingdom defines feasibility studies as those that are conducted in the early stages of the research process, before a pilot study, and aim to answer specific questions related to potentially conducting a given intervention research. Pilot studies are then defined as small versions of a main study that aim to determine whether all the components of the main study work together [12].

This study adopts the understanding of feasibility studies outlined by the National Institute of Health Research and focuses on the feasibility stage of intervention research, aiming to inform an RCT. The protocol has been written according to the Standard Protocol Item: Recommendations for Interventional Trials (SPIRIT) checklist [17], Medical Research Council Framework for Complex Interventions [16], and Template for Intervention Description and Replication (TIDieR) [18].

Feasibility studies have, by their nature, an exploratory design that aims to justify a full-scale effectiveness study [19]. In this study, we plan a flexible, convergent, and mixed methods exploratory design. A flexible exploratory design allows for changes during the course of the study, which can inform adjustments to the intervention and final intervention design [19], whereas a convergent mixed methods design allows the comparison of quantitative and qualitative data to confirm or disprove the findings of each approach [20]. Quantitative data will be collected from questionnaires and from the use data of the Technology-Optimized Practice Process in Nursing (TOPP-N) app [21]. Qualitative data will be collected from focus group interviews with participating nursing students, nurse preceptors, and nurse educators. Quantitative data will be analyzed using descriptive statistical methods [22]. We will calculate means, medians, SDs, skewness, and kurtosis [23,24] and report sample sizes and sample demographics [24], such as ages of participants, last completed education, and previous working experience in health care. A thematic analysis approach will be applied to qualitative data. The data will be coded, and the codes will be grouped into themes [25]. The quantitative and qualitative data will be integrated in a side-by-side comparison and interpreted in the Discussion section. Qualitative data will be reported and interpreted first and then compared with the quantitative findings to answer the research questions of the feasibility study [20].

Study Setting

The feasibility study will be conducted at 3 nursing homes, 1 in the county of Oslo, Norway, and 2 in the county of Kristiansand, Norway. The institutions were chosen based on previous cooperation and agreement in developing or testing the intervention.

Eligibility Criteria

The study will use a consecutive sampling strategy. Eligible participants include first-year undergraduate nursing students at LDUC and the University of Agder (UiA), nurse preceptors (registered nurses) and nurse educators at the participating institutions, nursing students in clinical practice, nurse preceptors and nurse educators guiding nursing students in clinical practice, and participants who are willing to provide signed informed consent.

Intervention Description

Intervention Name

The name of the intervention is Technology-Supported Guidance Model (TSGM).

Goal of the Elements Essential for the Intervention

The main element of the TSGM is the TOPP-N app [21], which helps students identify their need for guidance and stimulates reflection on their learning goal and what has been learned through their completion of electronic reports (e-reports).

Nurse preceptors and nurse educators can follow up on the progress of students and tailor their guidance based on their needs.

Nurse educators follow the students' guidance and intervene as necessary when automatically prompted by the guidance app.

A digital version of the Assessment of Clinical Education (AssCE) [26] mediates the summative evaluation of student performance during clinical practice with either in-person or virtual meetings.

Materials

Materials include the TOPP-N app [21] with a digital AssCE [27] module, accessible from mobile phones, tablets (Apple [iOS] or Android operating system), and web browsers (all standard browsers are supported).

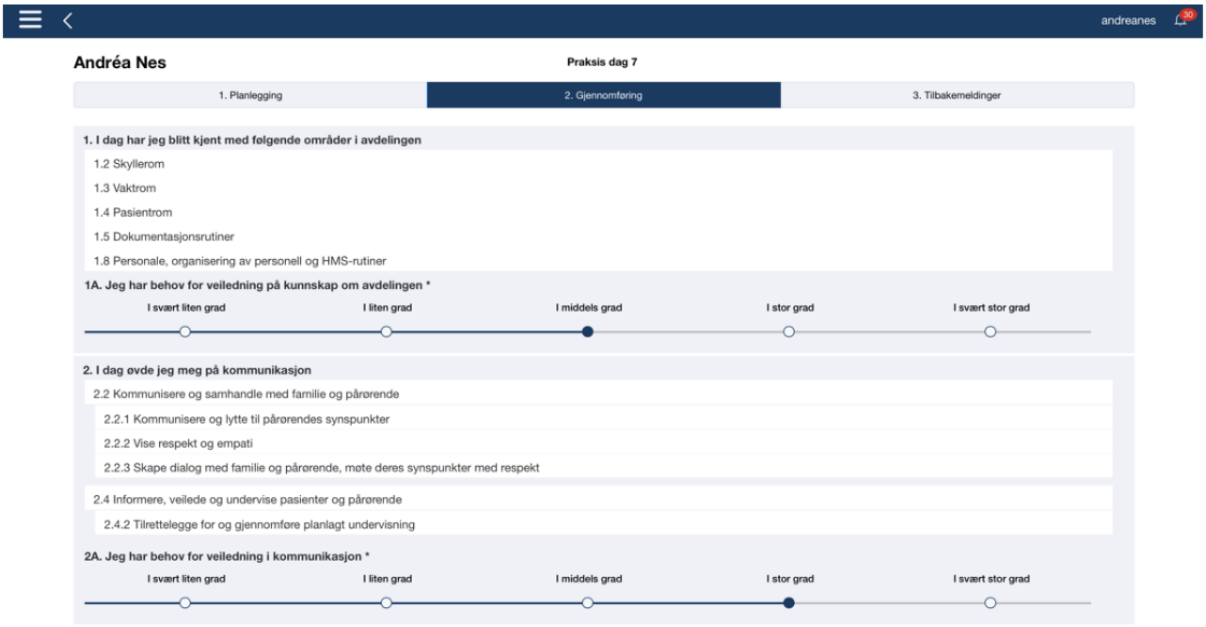
The app can be accessed from a web browser [21] or from Apple or Android systems downloadable from the Apple Store and Google Play, respectively. The informational materials in the training include flyers, posters, instructional videos, a Facebook group, and formal and informal meetings (Multimedia Appendix 1).

Videos can be found on the web [28].

Procedures

Nursing students use the TOPP-N app (Figure 1) [21] daily and must complete e-reports before and after their shift in clinical practice. The e-reports comprise checklists built on AssCE [27], each of which is accompanied by a scale on which the students indicate their need for guidance in specific learning activities. The checklist offers the possibility of further written elaboration.

Figure 1. Screenshot of the Technology Optimized Practice Process in Nursing app.



Nurse preceptors are required to give feedback on the daily performance of students and on completed e-reports through the TOPP-N app [21]. Feedback is given every day after the students have completed their reports.

Nurse educators follow the students' progress through the TOPP-N app [21] and intervene as necessary, when automatically prompted by the guidance app.

Summative assessment is done in the app with the help of the digital AssCE [27] in weeks 3 to 4 and 6 to 8 of the students'

clinical practice. The summative assessment is conducted as an individual meeting (physical or virtual) in which students, nurse preceptors, and nurse educators participate.

Delivery of Intervention

The intervention is delivered digitally by the TOPP-N app [21]. Daily guidance is delivered by nurse preceptors and, when necessary, by nurse educators. Summative assessment is delivered by nurse preceptors and nurse educators in collaboration with nursing students.

Modes, Place, and Frequency of Intervention Delivery

The intervention is delivered digitally through the TOPP-N app [21] and in virtual and face-to-face meetings between nursing students, nurse preceptors, and nurse educators, in 1 nursing home in Oslo, Norway, and 2 nursing homes in Kristiansand, Norway. It is delivered daily during 6 to 8 weeks of clinical practice.

Intervention Monitoring

The intervention is monitored digitally by oversight of the participants' activities and their interactions in the TOPP-N app [21].

Criteria for Modifying or Discontinuing an Intervention

Chan et al [17] highlighted the necessity of carefully considering when an intervention should be modified or stopped, and progression criteria are necessary elements of feasibility and pilot studies to evaluate whether a full-scale trial is viable [26]. Avery et al [29] proposed a traffic light system for progression criteria: green (go, indicates the criteria are met); amber (amend, indicates a need for change and adjustment); and red (stop, indicates that one should not move to a larger trial). Following Avery et al [29], the progression criteria are as follows: green (intervention proceeds as planned, and no problems are discovered), amber (problems are discovered and appropriate remedies are devised, and the intervention proceeds with close monitoring), and red (problems cannot be amended, and the intervention does not continue).

Adherence to the Intervention Protocol

Adherence describes the behavior of participants that aligns with the intervention and has been assigned to the participants [17]. Poor adherence may complicate statistical analysis, reduce the statistical power of the study, and result in underestimation of the efficacy of the intervention [30]. In this study, the guidance app has a built-in system that reminds participants to fill out e-reports and complete other required tasks.

Concomitant Activities and Other Activities Outside of Intervention

No limitations are imposed on the participants in relation to concomitant activities or other activities outside of the intervention.

Outcomes

The primary outcome is critical thinking. The secondary outcomes are self-efficacy, clinical learning environment, metacognition and self-regulation, technology acceptance, and competence of mentors. Table 1 provides a detailed overview of these outcomes.

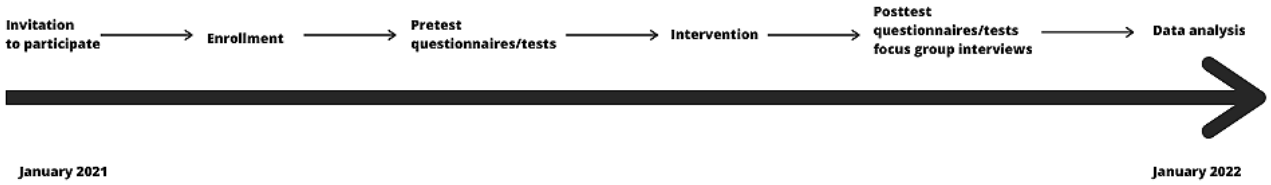
Table 1. Outcomes.

Outcomes	Definition
Primary outcome	
Critical thinking	Purposeful and self-regulatory judgment resulting in interpretation, analysis, evaluation, and inference efficacy [31].
Secondary outcomes	
Self-efficacy	Self-perceived ability to perform a task in a competent and effective manner [32,33].
Satisfaction with the clinical learning environment	A clinical learning environment that provides students with professional development and is a foundation for a supervisory relationship [34].
Technology acceptance	Acceptance or rejection of the use of new technology by users, with a focus on users' perceptions, attitudes, and intentions in the use of new technology [35].
Use of metacognitive processes	Use of metacognitive processes in clinical practice [36].
Mentors' competence	Level of competencies of mentors in clinical practice [37].

Participant Timeline

The participant timeline is shown in Figure 2.

Figure 2. Participant timeline.



Sample Size

Traditional sample size calculations are not suitable for feasibility studies, as their aim is not hypothesis testing [38,39], yet a feasibility study requires a proper sample size justification [39], especially in relation to its objectives [40]. Lancaster et al [40] have proposed 30 participants as *the rule of thumb*, but recommendations vary from 12 to 50 participants [41]. The current estimate for a sufficient number of participants, as described by Billingham et al [41], is between 12 and 50. For this study, we have decided to recruit a total of 32 nursing students (16 from LDUC and 16 from UiA) and 27 nurse preceptors (13 from LDUC and 14 from UiA).

Recruitment

The participants will be recruited from first-year undergraduate nursing students at LDUC, Oslo, Norway, and UiA Kristiansand, Norway. Drawing on the recommendations for recruitment in health research, the recruitment process will provide sufficient information about the overall study in meetings with the target group and will highlight its aim and benefits for participants [42]. To boost recruitment, we intend to maintain a prominent presence on social media.

Data Collection Methods

Data for the primary outcome will be collected using the Norwegian version of the Health Science Reasoning Test [43]. Data for the secondary outcomes will be collected using the Norwegian version of the Self-Efficacy in Clinical Performance [44], Clinical Learning Environment, Supervision and Nurse Teacher [45,46], Technology Acceptance Model 3 [47], Mentors Competence Instrument [37], and Self-Regulation and Metacognition in Clinical Practice instruments (self-created questionnaire for the purposes of this study).

In addition, data will be gathered from the TOPP-N app [21], and questionnaires will solicit self-reported sociodemographic data and evaluations of participation in the feasibility study. All data collection instruments will be administered digitally.

Data will also be collected through focus group interviews with nursing students, nurse preceptors, and nurse educators. The interviews will be conducted separately for each group using an interview guide and will last 60 minutes. One researcher will be the interviewer and the other a moderator. All focus groups will be conducted digitally using Zoom (Zoom Video Communications, Inc) videoconferencing version 5.6.5 [48]. Video from the interviews will be recorded, but only the sound file will be stored, and the video will be deleted at the end of the focus group interviews. Table 2 provides an overview of the data collection instruments. Textbox 1 presents the planned focus group interview topics.

Table 2. Overview of data collection instruments.

Measuring instrument	Characteristics of the instrument	Internal validity
HSRT[a]	• Multiple-choice test, 38 questions • Measurement of overall level of critical thinking • Measurement of detailed scores of analysis, interpretation, inference, evaluation, explanation, induction, deduction, and numeracy	Cronbach α of .76 for the overall instrument [49]
SECP[b]	• Measurement of self-efficacy on 37 items in 4 subscales: assessment, diagnosis and planning, implementation, and evaluation	Cronbach α for each item ranging from .90 to .92 [44]
CLES+T2[c]	• Measurement of satisfaction with the clinical learning environment on 45 items in three major themes: learning environment, supervisory relationship, and role of the nurse teacher	Cronbach α for each item ranging from .81 to .98 [45,46]
TAM 3[d]	• Measurement of acceptance of new technology on 37 items	Cronbach α for each item ranging from .77 to .87 [50]
SMCP[e]	• Measurement of level of use of self-regulation and metacognitive processes; measured on 11 items	Data not available
Sociodemographic data	• Year of birth, sex, last completed education, length of employment in health care with direct patient contact	Data not available
Evaluation of the feasibility study	• Evaluation of participation in the feasibility study	Data not available

[a]HSRT: Health Sciences Reasoning Test.

[b]SECP: Self-Efficacy in Clinical Performance.

[c]CLES+T2: Clinical Learning Environment, Supervision and Nurse Teacher.

[d]TAM 3: Technology Acceptance Model 3.

[e]SMCP: Self-Regulation and Metacognition in Clinical Practice.

Textbox 1. Planned topics in focus group interviews.

Nursing students

- Platform from which Technology Optimized Practice Process in Nursing (TOPP-N) has been used
- Use of TOPP-N
- Contribution of TOPP-N to performance of students in clinical practice
- Contribution of TOPP-N in receiving guidance from nurse preceptors
- Future needs for support when using TOPP-N
- Experience with filling out questionnaires and taking the critical thinking test
- Recruitment to intervention

Nurse preceptors

- Platform from which TOPP-N has been used
- Use of TOPP-N
- Contribution of TOPP-N in student guidance
- Comparison of using TOPP-N in guidance of students with earlier guidance without TOPP-N
- Future features and needs in TOPP-N
- Contribution to research which includes filling out questionnaire and time use
- Recruitment to intervention

Nurse educators

- Platform from which TOPP-N has been used
- Use of TOPP-N
- Contribution of TOPP-N in student guidance
- Comparison of using TOPP-N in guidance of students with earlier guidance without TOPP-N
- Future features and needs in TOPP-N
- Contribution to research which includes filling out questionnaire and time use
- Recruitment to intervention

Data Retention

To maintain interest in the study, announcements will be placed on the learning management platform Canvas (Instructure, Inc) [51], and nurse educators will closely communicate with students to support them as necessary. A dedicated support person will also be available to the participants.

Data Management

Participants' personal information and sociodemographic data and data from Self-Efficacy in Clinical Performance, Clinical Learning Environment, Supervision and Nurse Teacher, Technology Acceptance Model 3, and Self-Regulation and Metacognition in Clinical Practice will be collected by the Questback Management System (Questback Group AS) [52] and the results stored in the Questback system.

The Health Sciences Reasoning Test is conducted through the Insight Assessment testing system [43], a division of California Academic Press. The anonymous results are stored in the Insight Assessment system. A backup of personnel data and the results of the critical thinking test and other questionnaires will be stored on a Kingston DataTraveller 2000 USB stick with AES 256-bit encryption.

Methods of Analysis

For quantitative analysis, we will use SPSS, version 26 (IBM Corporation) [53]. For qualitative analysis, we will use MAXQDA Analytics Pro 2020 version 9 (VERBI GmbH) [54].

Program Theory

The intervention is theoretically based on the concept of metacognition, which is regarded as a higher-order thinking skill and describes the cognitive process of *thinking about one's own thinking* [55]. It is the ability to be aware of, reflect on, and use strategies during cognitive tasks. People who demonstrate high metacognitive abilities tend to be more focused, thoughtful, and strategic in making decisions and solving problems [56]. Thus, they view their own competence as a dynamic and formable entity, which motivates them to learn from previous knowledge and experiences and seek new solutions. Metacognition is often framed as a highly cognitive skill; however, there is a high correlation between metacognition and self-regulation, which means that metacognition also depends on motivational elements, such as goal setting, determination, and attention control [55,57].

Metacognition is used as a theoretical framework for TSGM because research shows a close interrelationship between metacognition and critical thinking [58]. Thus, we assume that, if the guidance app supports metacognitive skills of students in clinical practice, it will also have a positive effect on their critical thinking skills. The interrelationship between the two concepts can be traced to the importance of self-monitoring and self-reflection in understanding information and thinking through discussions regarding learning and problem-solving [59].

More specifically, the intervention will build on the principles of the metacognitive cycle, which comprises three main phases that together make up a metacognitive process. The first phase is planning and setting goals. Goal setting is an important part of metacognition, as it prepares students to be attentive, aware, and focused on the learning objectives and strategies they will use in pursuing them.

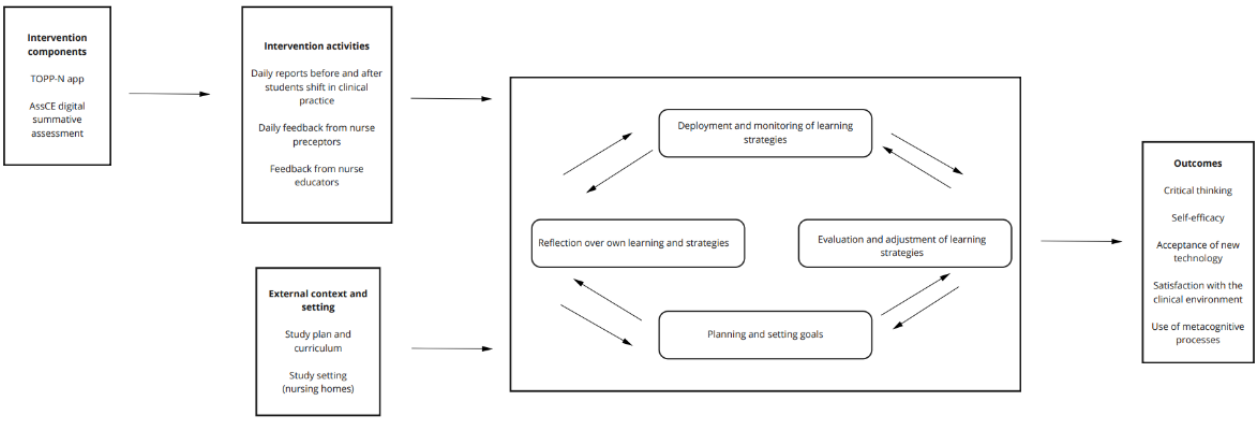
Experts often take more time than novices do in preparing to solve a problem [60]. As metacognitive masters in their domain, they show the wisdom of making considerable preparation before entering the second phase of the cycle.

In the second phase, the planned strategies are applied in the situation. Here, it is important not to be constrained by the planned actions and to maintain self-awareness and higher-order thinking during the activity so that ongoing decisions can be adapted to situational demands.

The third phase occurs after the situation has played out. Now, it is important to engage in critical self-evaluation and reflect on how the applied strategies dealt with situational demands and contributed to achieving the goals established in the first phase. Furthermore, self-evaluation will provide invaluable information when once again entering the first phase and planning new goals and strategies. An important part of this process is the feedback from nurse preceptors, which further stimulates critical self-evaluation and reflection.

These phases may be further influenced by factors such as task constraints, beliefs about learning, awareness of one's own strengths and weaknesses, and individual motivation. Research also shows that metacognition, similar to most cognitive abilities, is not a wholly general ability [55], meaning that advanced metacognitive abilities are not necessarily transferred from one domain to another and that they should be practiced in the relevant context. Figure 3 is a diagrammatic representation of the program theory.

Figure 3. The program theory. AssCE: Assessment of Clinical Education; TOPP-N: Technology-Optimized Practice Process in Nursing.



Research Ethics Approval

The study was approved on December 21, 2020, by the Norwegian Centre for Research Data (reference number: 338576).

Changes in Protocol

Protocol modifications will be communicated in subsequent publications in research journals.

Ethics

Each participant signs a written informed consent form. Informed consent is obtained digitally through Questback [52]. The students are thoroughly informed (both verbally and in writing) that participation or nonparticipation in the research project will not affect their study progression or the evaluation of their performance. None of the researchers participating in this research study was involved in any form of formal teaching, evaluation, or student follow-up. This is important in preventing potential conflicts of interests [17].

Confidentiality of Information

On agreeing to participate, each participant receives a numerical code, which is their identifiable information. The numerical codes will be kept separately from the actual list of the participants.

Dissemination Policy

According to Craig et al [16], results should be disseminated actively and targeted in a way that makes them easily understandable and accessible. The research findings will be disseminated by publishing research articles in open-access research journals. In addition, the research team of the study will ensure a strong presence on social media and promote the publication of relevant articles in the daily press, where the findings and news about the research results will be disseminated in a manner easily understandable to a wider audience.

Conference participation is also part of the dissemination strategy of the study.

Results

The feasibility study was completed in March of 2021. Quantitative data (from questionnaires) were collected at baseline, before the feasibility study began, and after its completion. We collected qualitative data (focus group interviews) in April of 2021. Table 3 provides a detailed timeline of the further stages of the analysis. This study is expected to conclude in January 2022.

Table 3. Detailed timeline of further stages of analysis.

Data analysis	Timeline
Quantitative data	
Calculation of means, medians, SDs, skewness, kurtosis	August 2021
Reporting of sample sizes and sample demographics	August 2021
Qualitative data	
Transcription of focus group interviews	June to July 2021
Analysis of focus group interviews	August to October 2021
Integration of qualitative and quantitative data	November to January 2022

Discussion

General

Critical thinking is an essential skill set in nursing [61], and previous research underscores the need for more quantitative approaches to critically evaluate how critical thinking skills are developed, especially among nursing students in a clinical setting [62].

Significance of Results

The feasibility study offers the advantage of testing and fine-tuning certain parts of the main study [63].

Limitations

A limitation of this study is that the intervention has many complex parts that require close monitoring and follow-up, and the feasibility study runs alongside the control group arm of the trial. Consequently, it may not be possible to use all the results to fine-tune the intervention and the trial (eg, the choice of outcome or data collection instruments). The decision to run the feasibility study alongside the control group arm of the trial was made for practical reasons related to how the curriculum and clinical practice are organized, particularly in the context of the influence of the COVID-19 pandemic on the operation of clinical practice.

Conclusions

The results will determine the acceptability and suitability of the intervention, as well as the information collection strategy and outcome measures for a technology-supported guidance model for nursing students in clinical practice, as well as dropout causes, adherence challenges, and retention.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Poster used in participant recruitment.
[PDF File (Adobe PDF File), 446 KB - resprot_v10i10e31646_app1.pdf]

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Abbreviations

AssCE: Assessment of Clinical Education
LDUC: Lovisenberg Diaconal University College
TIDieR: Template for Intervention Description and Replication
TOPP-N: Technology-Optimized Practice Process in Nursing
TSGM: Technology-Supported Guidance Model
UiA: University of Agder

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Protocol

Diagnosis and Management of Traumatic Subarachnoid Hemorrhage: Protocol for a Scoping Review

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Abstract

Background: Globally, 69 million people suffer from traumatic brain injury (TBI) each year and TBI is the most common cause of subarachnoid hemorrhage (SAH). Traumatic SAH (TSAH) has been described as an adverse prognostic factor leading to progressive neurological deterioration and an increase in morbidity and mortality, but there are a limited number of studies which evaluate recent trends in the diagnostic and management of SAH in the context of trauma.

Objective: The objective of this scoping review was to understand the extent and type of evidence in relation to the diagnostic criteria and management of TSAH.

Methods: This scoping review will be conducted in accordance with the Joanna Briggs Institute methodology for scoping reviews. A 3-step search strategy (an initial limited search in PubMed and Scopus databases; a main search of EMBASE, Web of Science, EBSCO, MEDLINE; and manual searches of reference lists of included articles) will be utilized. The search will be limited to studies with human participants and published in English, Spanish, and French between 2005 and 2020. This review will consider studies of adolescent and adult patients with SAH secondary to trauma. Study selection will be performed by 2 authors (DG and LF) in a 2-phase process; if any disagreement arises, a third author (AR) will be consulted. Data to be extracted from each study will include population, intervention, comparator and outcome measures, and a summary of findings. Citation screening, full-text review, risk of bias assessment, and extraction of study characteristics and outcomes will be carried out using a web-based software platform that streamlines the production of scoping reviews.

Results: Ethics approval is not required for this systematic review, as there will be no patient involvement. The search for this systematic review commenced in December 2020, and we expect to publish the findings in early 2021. The plan for dissemination is to publish review findings in a peer-reviewed journal and present findings at conferences that engage the most pertinent stakeholders.

Conclusions: This scoping review will serve as an initial step in providing more evidence for health care professionals, economists, and policymakers so that they might devote more resources toward this significant problem affecting both health and economic outcomes worldwide.

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KEYWORDS

diagnostic criteria; management; neurosurgery; neurotrauma; SAH; scoping review; TBI; trauma

Introduction

It is estimated that, globally, 69 million people (95% CI 64-74 million) have a traumatic brain injury (TBI) each year [1]. High-income countries have nearly 3 times more cases than low-and middle-income countries (LMICs) [1]. This is relevant because TBI is the most common cause of subarachnoid hemorrhage (SAH). Thus, traumatic subarachnoid hemorrhage (TSAH) is a common finding in moderate and severe TBI (sTBI), because it occurs in 33%-60% of patients [2,3]. Road traffic accidents, falls, and violence are the main contributing factors to sTBI, and the majority of victims are in the prime of life (aged 15-44) and leading contributors to the country's gross domestic product (GDP). Thus, a country's economic security is affected by sTBI, and the country should have a vested interest in reducing its prevalence [4].

Although it is necessary to understand this condition's pathophysiology more completely, some theories have been described in animal studies that could largely explain the clinical course of TSAH. These theories are principally concerned with the phenomenon of traumatic vasoconstriction, which contributes to secondary ischemic damage and has a variable incidence range of 19%-68%. Marmarou and associates [5] and Thomas and colleagues [6] used a rat model to describe the significant increase of intracranial pressure and mean arterial blood pressure changes that occur as a compensatory mechanism to maintain normal cerebral perfusion pressure [2].

TSAH has been described as an adverse prognostic factor leading to progressive neurological deterioration and increased morbidity and mortality. This is because of its related events of vasospasm, dyselectrolytemia, pituitary dysfunction, hypoxia, intracranial hypertension, and hydrocephalus [3].

Current resources aim to understand the diagnosis and treatment of patients with SAH according to the severity degree of the trauma. The goal is to use this information to evaluate the cost-effectiveness of current management, reduce the length of stay, and redirect the use of already limited resources [7]. Recently published studies have mentioned that patients with SAH secondary to mild TBI (mTBI) have a lower risk of clinical deterioration and that surgical intervention [8], along with the routine implementation of computed tomography scans, mandatory neurosurgery consultations, and high-intensity observations, is not necessary in most cases [7,8].

TSAH is a public health problem of significant proportions because of the global burden of disease and its disproportionate effect on LMICs. While research has made it possible to improve the use of resource-stratified clinical interventions, it is not enough [7]. Economies are dependent on fiscally active adults, and TSAH stunts the growth of GDP in LMICs. The implications, then, lie beyond the scope of medicine and must be taken up by economists and politicians.

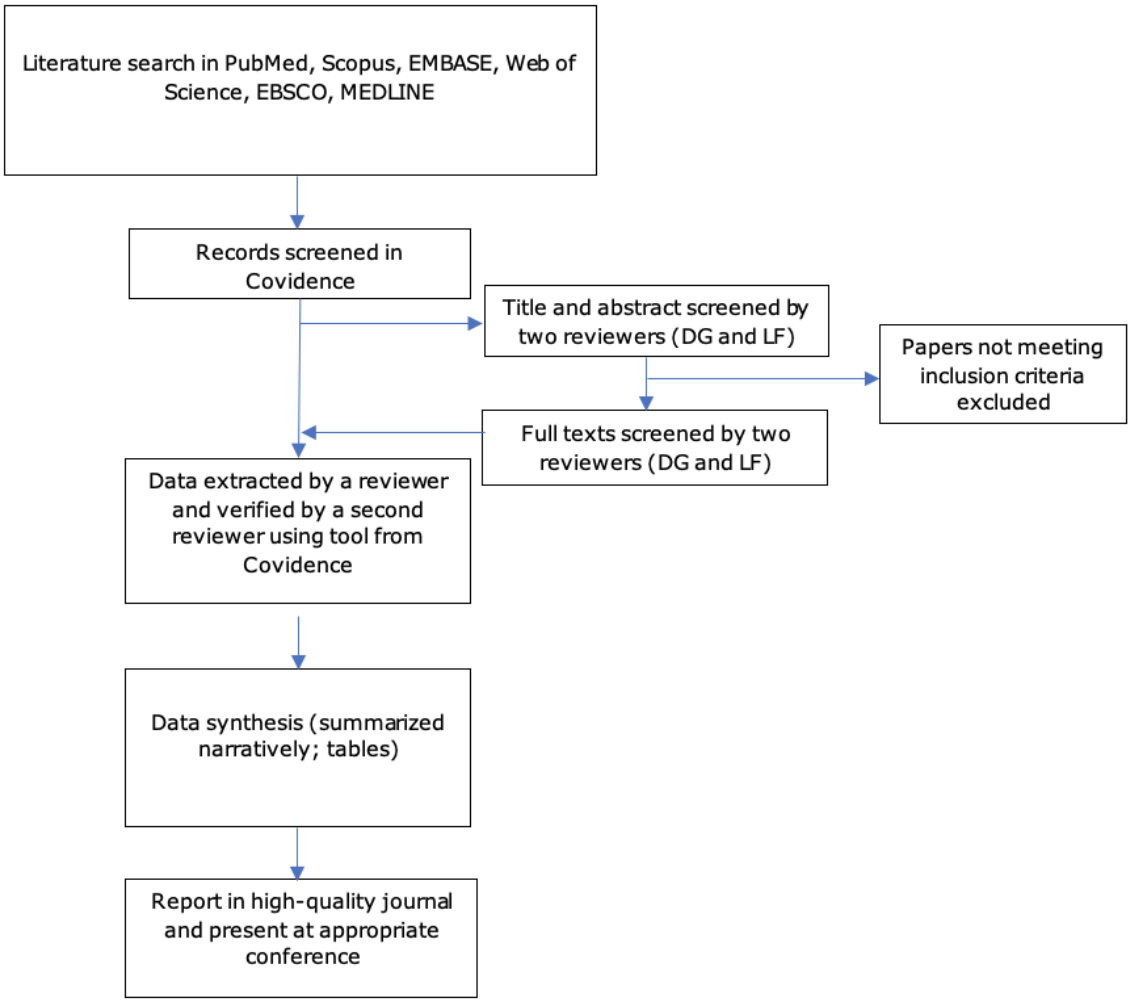
The bone structure, clinical outcomes, and pathophysiology of TBI in the pediatric population differ from adults and thus were excluded from the review [9]. Therefore, the objective of this scoping review is to develop a better understanding of TSAH in the adult population. This scoping review will serve as an initial step in providing more evidence for health care professionals, economists, and policymakers so that they might devote more resources toward this significant problem affecting both health and economic outcomes worldwide.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted, and no current or under way systematic reviews or scoping reviews on the topic were identified.

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [10]. The proposed methodology is presented in Figure 1.

Figure 1. Summary of search strategy process.



Search Strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE and Scopus 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 to develop a full search strategy for PubMed and Scopus. A full search strategy for both MEDLINE and SCOPUS is detailed in Multimedia Appendices 1 and 2, respectively. In the second phase of the search, a final search strategy will be adopted for each information source. The reference lists of all selected studies will be screened for additional studies during the third phase of the search.

Studies published in English, Spanish, and French between the years 2005 and 2020 will be included.

Review Question and Keywords

> *What is the current evidence on the diagnostic and management protocols of traumatic subarachnoid hemorrhage?*

The following keywords will be used: diagnostic criteria; management; neurosurgery; neurotrauma; SAH; scoping review; TBI; trauma

Inclusion Criteria

Participants

Studies of adult and teenage (>15 years old) patients will be included. All studies of pediatric patients (<15 years old) will be excluded.

Concept

The concept of interest for the proposed scoping review is studies of subarachnoid hemorrhage secondary to TBI. This will include, but not be limited to, population, intervention, validation status, method of study development, whether the study is consensus or evidence based in addition to the comparator and outcome measures. All studies focused on non-TSAH will be excluded.

Context

The review will be limited to studies conducted between 2005 and 2020 in keeping with the objective to evaluate recent trends.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies. Besides,

analytical observational studies, including prospective and retrospective cohort studies, case–control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports, and descriptive cross-sectional studies for inclusion.

Qualitative studies will also be considered that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, qualitative description, and action research.

In addition, systematic reviews that meet the inclusion criteria will be considered, depending on the research question.

Text and opinion papers will also be considered for inclusion in this scoping review.

Information Sources

The databases to be searched include PubMed, Scopus, EMBASE, Web of Science, EBSCO, and MEDLINE.

Study/Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNoteX9 (Clarivate Analytics). The citations will then be imported into Covidence online software (Veritas Health Innovation) for screening. Two independent researchers (DG and LF) will examine titles and abstracts for inclusion. The full text of selected studies will be retrieved and assessed. Full-text studies that do not meet the inclusion criteria will be excluded, and the reasons for exclusion will be provided in an appendix in the final scoping review. Any disagreements that arise between the researchers during either title and abstract screening or full-text screening will be resolved through discussion, or with a third reviewer (AR). Included studies will undergo a process of data extraction. The results of the search will be reported in full in the final article and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.

Data Extraction

Data will be extracted from the papers included in the review by 2 independent researchers (DG and LF) using the data extraction instrument (Multimedia Appendix 3). The following information will be extracted from the articles: (1) study title; (2) aim; (3) country; (4) methodology; (5) duration; (6) participant characteristics; (7) intervention; (8) outcome measures; (9) summary of findings; and (10) recommendations for future development.

The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included study. Modifications will be detailed in the full scoping review report. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (AR). Authors of papers will be contacted to request missing or additional data, where required.

Data Analysis and Presentation

The extracted data will be presented in tabular form and as a narrative summary that aligns with the aim of this scoping review. The table will report: (1) distribution of studies by countries of origin/study design; (2) participants/sample size; (3) intervention studied; (4) outcome measure; and (5) summary of findings. This table may be further refined at the review stage. Graphical representations may be used, including bar charts, line charts, pie charts, and diagrams. A narrative summary will accompany the tabulated or charted results and will describe how the results relate to the review's objectives.

Results

No ethical approval will be required, as this review is based on already published data and does not involve interaction with human participants. The search for this systematic review commenced in December 2020, and we expect to publish the findings in early 2021. The plan for dissemination, however, is to publish the findings of the review in a peer-reviewed journal and present findings at high-level international conferences that engage the most pertinent stakeholders.

Discussion

This protocol has been rigorously developed and designed specifically to identify and summarize the available literature regarding the diagnosis and management of TSAH. The results from this scoping review will serve as an initial step to provide greater evidence for health care professionals, economists, and policymakers to encourage them to devote more resources toward this significant problem affecting both health and economic outcomes worldwide. Preliminarily, we have observed that there is a paucity of information available for TSAH associated with sTBI and the evidence on TSAH. Furthermore, the evidence on mTBI greatly outweighs that which is available for TSAH and sTBI.

Acknowledgments

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Authors' Contributions

AR conceived the review. DG and LF designed the review. DG and LF refined the review design and were involved in the initial drafting of the manuscript. All authors were involved in subsequent draft manuscript reviews and updates and approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PubMed search strategy.
[DOCX File , 13 KB - resprot_v10i10e26709_app1.docx]

Multimedia Appendix 2
Scopus search strategy.
[DOCX File , 13 KB - resprot_v10i10e26709_app2.docx]

Multimedia Appendix 3
Data extraction instrument.
[DOCX File , 13 KB - resprot_v10i10e26709_app3.docx]

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Abbreviations

GDP: gross domestic product
JBI: Joanna Briggs Institute
LMIC: low-and middle-income country
mild TBI: mild traumatic brain injury
SAH: subarachnoid hemorrhage
sTBI: severe traumatic brain injury
TBI: traumatic brain injury
TSAH: traumatic subarachnoid hemorrhage

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Protocol

Function and Emotion in Everyday Life With Type 1 Diabetes (FEEL-T1D): Protocol for a Fully Remote Intensive Longitudinal Study

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Abstract

Background: Although short-term blood glucose levels and variability are thought to underlie diminished function and emotional well-being in people with type 1 diabetes (T1D), these relationships are poorly understood. The Function and Emotion in Everyday Life with T1D (FEEL-T1D) study focuses on investigating these short-term dynamic relationships among blood glucose levels, functional ability, and emotional well-being in adults with T1D.

Objective: The aim of this study is to present the FEEL-T1D study design, methods, and study progress to date, including adaptations necessitated by the COVID-19 pandemic to implement the study fully remotely.

Methods: The FEEL-T1D study will recruit 200 adults with T1D in the age range of 18-75 years. Data collection includes a comprehensive survey battery, along with 14 days of intensive longitudinal data using blinded continuous glucose monitoring, ecological momentary assessments, ambulatory cognitive tasks, and accelerometers. All study procedures are conducted remotely by mailing the study equipment and by using videoconferencing for study visits.

Results: The study received institutional review board approval in January 2019 and was funded in April 2019. Data collection began in June 2020 and is projected to end in December 2021. As of June 2021, after 12 months of recruitment, 124 participants have enrolled in the FEEL-T1D study. Approximately 87.6% (7082/8087) of ecological momentary assessment surveys have been completed with minimal missing data, and 82.0% (82/100) of the participants provided concurrent continuous glucose monitoring data, ecological momentary assessment data, and accelerometer data for at least 10 of the 14 days of data collection.

Conclusions: Thus far, our reconfiguration of the FEEL-T1D protocol to be implemented remotely during the COVID-19 pandemic has been a success. The FEEL-T1D study will elucidate the dynamic relationships among blood glucose levels, emotional well-being, cognitive function, and participation in daily activities. In doing so, it will pave the way for innovative just-in-time

interventions and produce actionable insights to facilitate tailoring of diabetes treatments to optimize the function and well-being of individuals with T1D.

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KEYWORDS

ecological momentary assessments; type 1 diabetes; patient-centered outcomes research; actigraphy; ambulatory monitoring; continuous glucose monitoring; EMA; diabetes; patient-centered outcome; outcome; monitoring; function; emotion; longitudinal; well-being

Introduction

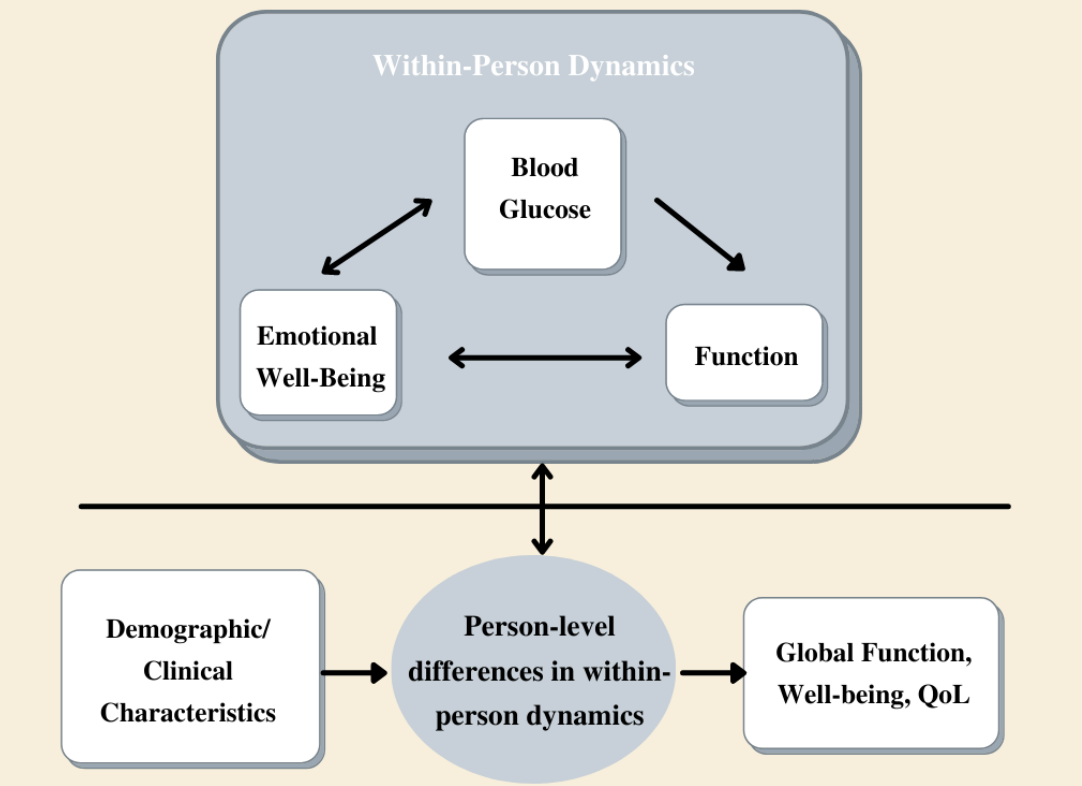
Background

Type 1 diabetes (T1D) is an autoimmune disease affecting about 1.6 million people in the United States [1]. T1D is characterized by a near absolute insulin deficiency, requiring intensive management to minimize fluctuations in blood sugar levels. Successfully managing T1D involves consistent ongoing attention to numerous self-care tasks that can be complex and challenging, including monitoring blood glucose levels, taking insulin, managing acute complications, and maintaining supplies and equipment. Such intensive management is needed because blood sugar fluctuations can have a profound impact on everyday life, including swings in emotional states, changes in cognitive functioning, and disruptions to participation in daily activities [2-9]. However, empirical data on these complex relationships within the stream of day-to-day life are limited, as research, to date, has primarily relied on (1) hemoglobin A_{1c} (HbA_{1c}) as a measure of blood glucose, which does not capture short-term blood glucose levels and variability [10] and (2) global, retrospective reports of mood, function, and well-being, which do not afford the ability to examine short-term dynamics in subjective experiences and functioning and are often biased by current states and recall problems. A recent review notes a lack of definitive empirical evidence, calling for more rigorous methodology to investigate relationships between glucose variability and mood [11]. This study addresses the call for increased rigor by employing blinded continuous glucose monitoring, accelerometry, ambulatory cognitive tasks, and ecological momentary assessment (EMA) to uncover dynamic associations among blood glucose levels, function, and emotion. Understanding these complex momentary relationships will facilitate tailoring of treatment strategies and development of adaptive, just-in-time interventions to maximize the quality of life among individuals living with T1D.

Study Aims

This paper presents the rationale and design of the Function and Emotion in Everyday Life with Type 1 Diabetes (FEEL-T1D) project (NIH/NIDDK #1R01DK121298-01). FEEL-T1D utilizes intensive longitudinal data collection with EMA surveys, ambulatory cognitive testing, and wearable technology (accelerometer, continuous glucose monitor [CGM]) to address 3 primary aims, as depicted in Figure 1. First, we examine within-person dynamic relationships between various measures of blood glucose (acute blood glucose level, glycemic excursions, glycemic variability, time-in-range/hypoglycemia/hyperglycemia), function (self-reported daily life activity performance, objective cognitive function, physical activity derived from accelerometers), and emotional well-being (positive and negative affect, stress, diabetes distress). Second, we evaluate how demographic and clinical characteristics predict individual differences in these within-person effects to inform tailoring of interventions and glycemic targets for population subgroups. Third, we investigate which aspects of these short-term dynamics most impact overall well-being, functioning, and quality of life. In doing so, the overall goal of FEEL-T1D is to provide actionable insights for researchers, clinicians, and patients to meaningfully improve health and well-being of people with T1D.

Figure 1. Conceptual diagram of the primary aims of the FEEL-T1D (Function and Emotion in Everyday Life with Type 1 Diabetes) study. QoL: quality of life.



COVID-19 Impact

The FEEL-T1D study was on the brink of initiating recruitment and data collection in March 2020, when stay-at-home orders in California and New York related to the coronavirus (COVID-19) pandemic required us to reconfigure our planned data collection protocol. Most notably, enforced social distancing practices meant that the planned in-person enrollment, baseline, and follow-up participant visits needed to be conducted fully remotely. Necessary adaptations included maximizing the use of available technology, making use of mailing and delivery services, and selecting measurement tools that were feasible to administer remotely.

Methods

Overview of the Study Design

In the FEEL-T1D project, adults with T1D are asked to complete 14 days of intensive longitudinal data collection using blinded CGM, EMA surveys, ambulatory cognitive tasks, and accelerometer wear. Over 14 days, participants complete 5-6 momentary surveys per day at 3-hour intervals. The first and last surveys of the day ask additional questions to capture information about other constructs on a daily basis. Participants are also asked to complete a baseline survey battery prior to the 14-day period and a follow-up survey battery immediately after the 14 days.

Participant Recruitment and Eligibility

We are recruiting participants from 3 clinical sites in the greater Los Angeles and New York City metropolitan areas, which collectively serve nearly 2400 ethnically and socioeconomically diverse adults with T1D. Participant eligibility criteria are outlined in Textbox 1. Eligibility criteria were selected to ensure that participants have the ability to complete study procedures and do not have conditions other than diabetes that could significantly influence blood glucose levels. We are seeking to recruit and collect data from a racially, ethnically, and socioeconomically diverse sample to ensure inclusion of underrepresented populations. Furthermore, we aim to enroll participants by using a wide range of diabetes treatment approaches (ie, injections, open-loop insulin pump, closed-loop insulin pump, personal CGM users, and nonusers) to include these regimen differences as potential covariates in analyses. Given the rapidly accelerating uptake of diabetes technologies [12,13] and well-documented differences in clinical outcomes dependent on treatment regimens [14,15], we are eager to investigate whether diabetes technology use has similar implications for mood and functional outcomes. Because starting a new diabetes treatment strategy can influence one's emotional experiences and take time to develop into a routine, we require that participants be on a stable diabetes therapy for at least 3 months in order to allow time to adjust to the new regimen. For similar reasons, we require that participants taking psychiatric medications be on a stable medication regimen for at least 2 months prior to participation.

Textbox 1. Eligibility criteria for the participants in the FEEL-T1D (Function and Emotion in Everyday Life with Type 1 Diabetes) study.

Inclusion criteria

- Age of 18-75 years (inclusive) at the time of enrollment
- Written and oral proficiency in English or Spanish
- Diagnosis of type 1 diabetes for ≥1 year
- On stable diabetes therapy for >3 months
- >1 month of experience using smartphone (including basic tasks such as texting, emailing, or use of apps)
- Sufficient visual acuity and manual dexterity to manipulate smartphone apps used for data collection
- If on psychiatric medication, on stable medication regimen for >2 months
- Willing and able to complete study procedures
- Participants will be in their normal routine (eg, no unusual or significant events planned during the 2-week data collection period)

Exclusion criteria

- Any significant developmental, cognitive, or behavioral conditions (eg, dementia, psychosis) that inhibit completion of study procedures (per observation or medical chart review).
- Currently planning pregnancy, pregnant, or have been breastfeeding for <6 months
- Known adhesive allergy or contact dermatitis that precludes wearing study devices
- Taking systemic corticosteroids (unless on chronic, stable dose at Principal Investigator discretion)
- Planned medical procedure, magnetic resonance imaging, radiography, computed tomography scan, or high-frequency electrical heat (diathermy) treatment during study participation
- Current enrollment in another study that may impact variables assessed in FEEL-T1D
- Currently or within past 14 days has infection or other significant illness (including COVID-19)
- Any other condition that, per study physician review, could interfere with study participation or blood glucose patterns

During the COVID-19 era, the criteria of "experience using a smartphone" and "no illness within the past two weeks" were deemed especially important. Smartphone use was not only evidence that they would be able to follow through with the smartphone (EMA and ambulatory cognitive testing) portion of the study but also an indirect indicator of basic technical ability. Because of the additional technology used in the adapted data collection procedures such as videoconferencing as well as the lack of hands-on training in using the study-provided smartphone, this ability was especially important. In terms of the illness criteria, we were concerned about the possibility of transmitting COVID-19 through incidental exposure during mailing, as well as its impact on participants' blood glucose levels, mood, and daily activities. Therefore, we decided that any participant who was ill but otherwise eligible for the study needed to be recovered from their illness (irrespective of whether the illness was confirmed to be COVID-19) for at least 2 weeks prior to study participation.

Recruitment and Retention

Participating sites recruit eligible patients remotely through mailings, phone calls, email invitations, and health provider referrals; previously planned in-person recruitment strategies were eliminated due to COVID-19. Research coordinators have access to patients' medical charts and contact information at their clinical sites, conduct eligibility screening based on participants' self-report and medical chart data when relevant and available, and enroll participants over the phone or through videoconferencing. In the case of participants for whom medical chart data is unavailable, eligibility is verified through objective sources (eg, medical records from outside the health system) or through consultation with a study physician prior to study enrollment. The following strategies are being used to maximize retention: (1) daily text messages to provide feedback about survey completion; (2) phone check-ins to resolve questions, address concerns, and provide encouragement; (3) collecting multiple forms of contact information for each participant; and (4) offering graduated stipends where the maximum amount is earned with full completion of the study. Participants earn up to US $200 for completion of all study procedures: US $25 for baseline procedures (disbursed after the baseline call), US $50 for each week that more than 75% of momentary surveys are completed (up to US $100 disbursed after the 2 weeks of data collection), and US $75 for the follow-up procedures and returning the study equipment. In situations where extended data collection is needed owing to reasons such as technical difficulties, additional reimbursement is offered.

Remote Data Collection Procedures

Data Collector Training

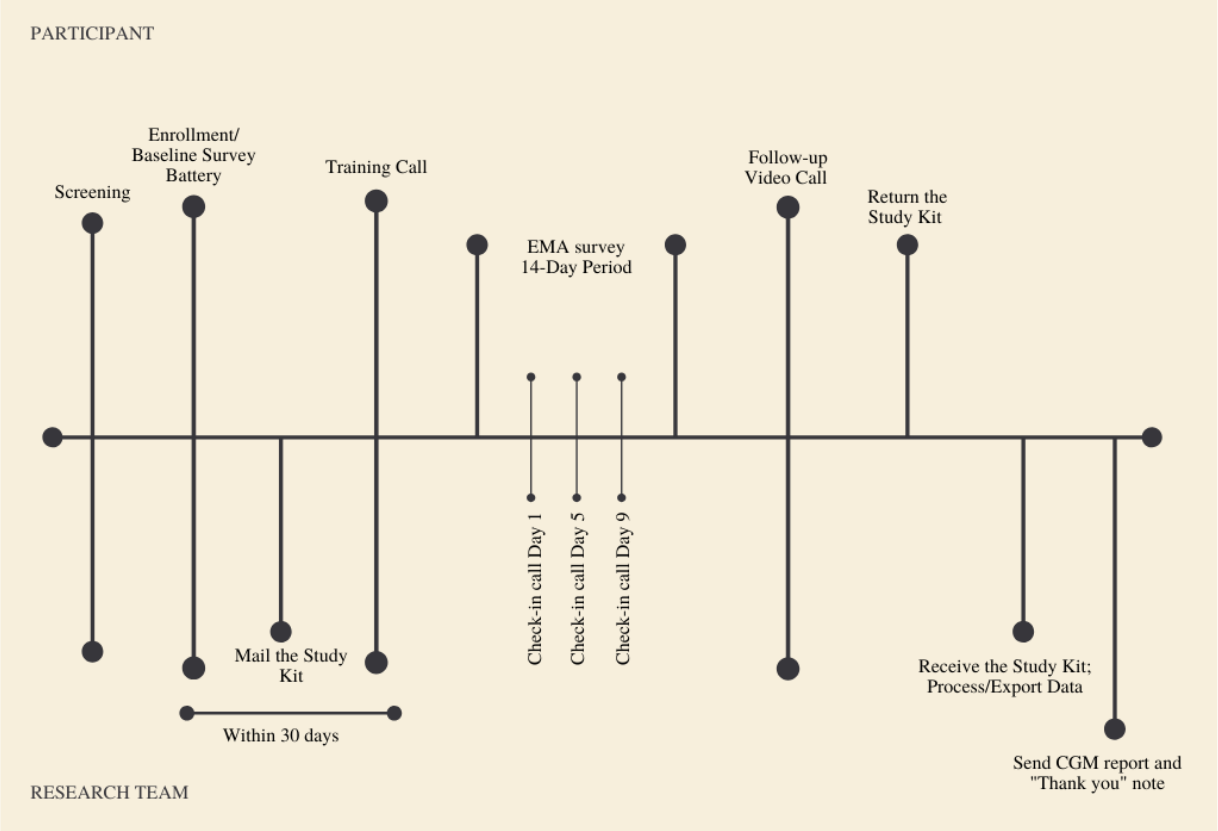
Prior to carrying out data collection, research coordinators completed approximately 30 hours of training to master the study procedures and technology. Training materials included video guides and digital manuals. Owing to social distancing requirements, research coordinators needed to become familiar with the technologies that are not part of our previously planned in-person data collection procedures, including

videoconferencing software, web-based survey programs, and Google Voice. Additionally, they needed to become accustomed to shipping procedures for study equipment, including disinfecting protocols to minimize the spread of COVID-19. Prior to initiating data collection with participants, research coordinators completed the data collection procedures themselves and conducted a data collection pilot with study team members posing as participants to refine data collection procedures.

Screening, Enrollment, and Baseline Data Collection

Figure 2 provides an overview of our remote data collection procedures. Participants who are identified as provisionally eligible per medical chart review are contacted by the study team; those who express interest in the study complete a screening questionnaire over the phone. If found to be eligible and interested in the study after the screening, study enrollment can take place. Enrollment paperwork was adjusted to be fully remote. The e-consent framework in research electronic data capture (REDCap), our online data capture platform, is used to record the digital signatures for study enrollment forms, including informed consent, Health Insurance Portability and Accountability Act (HIPAA) authorization, a Loaner Devices Agreement, and Study Stipend form [16]. Lastly, participants complete a baseline survey battery administered via the REDCap survey administration tool.

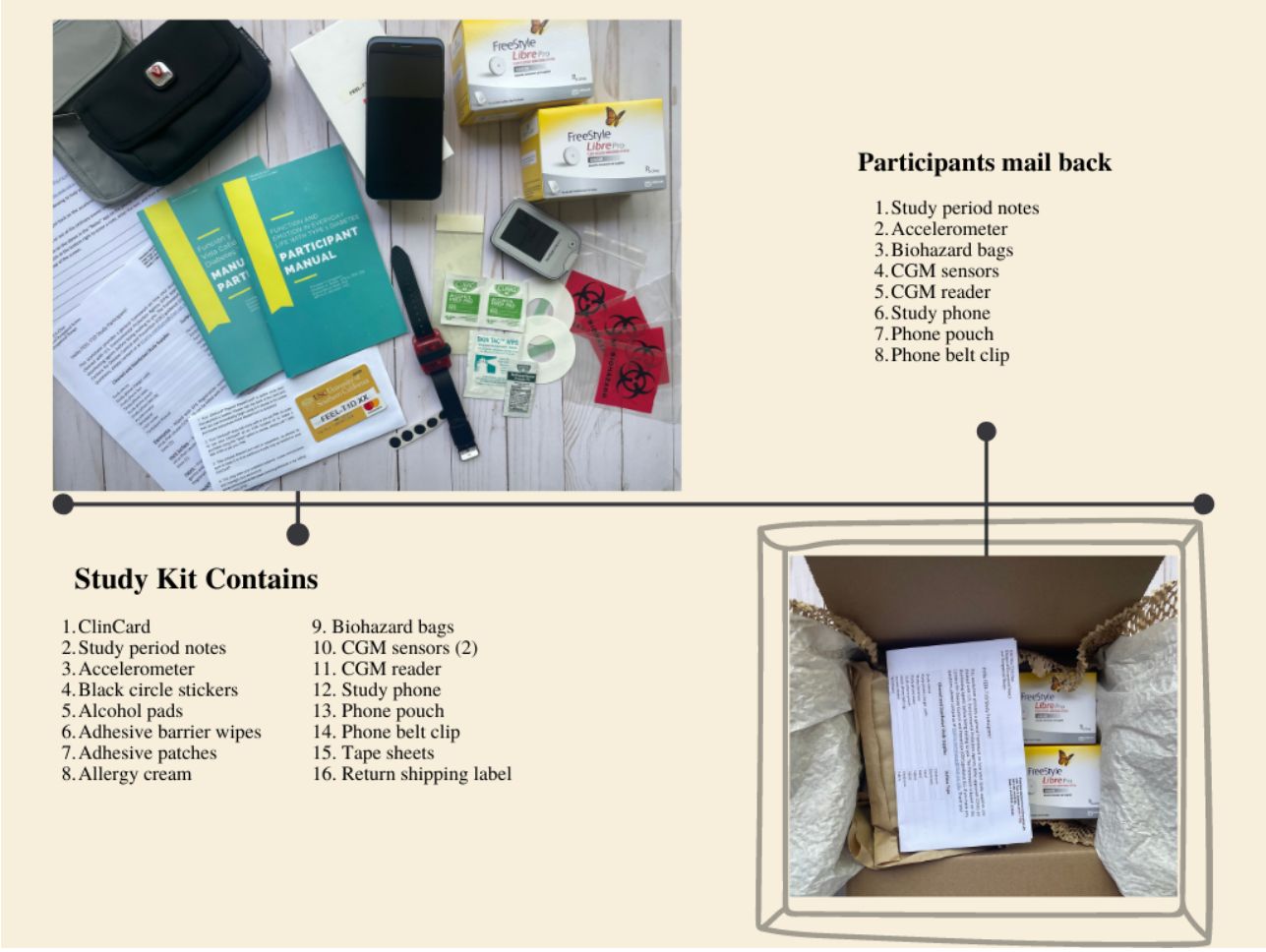
Figure 2. Remote data collection procedures. CGM: continuous glucose monitor; EMA: ecological momentary assessment.



Shipping of the Study Materials

To begin the EMA portion of the study, a box of study materials is shipped to the participants, as shown in Figure 3. These materials include 2 Abbott FreeStyle LibrePro Flash Glucose Monitoring System CGM sensors (a primary sensor and a backup if the first sensor falls off) and a CGM reader (used to activate the sensor; Abbott Diabetes Care), a wrist-worn wGT3X-BT accelerometer (Actigraph), a smartphone (Xiaomi Mi A1) with necessary apps preinstalled and phone accessories, a participant manual, a ClinCard onto which study stipends are loaded, various materials to enhance wearability of devices (eg, adhesive patches, adhesive barrier wipes, allergy relief spray to prevent skin irritation, hydrocortisone cream in the event of an allergic reaction), and materials to return the package after data collection. We are mindful of the possibility that study materials mailed to participants may be lost or damaged and have adjusted our data collection protocol to minimize this risk. Participants are asked to complete baseline surveys before study materials are shipped to them, thereby providing a general indication of their ability and commitment to complete study procedures before sending the materials. Additionally, participants do not receive their final stipend disbursement until all study devices are received in a good working condition, thereby providing a financial incentive to return materials in a timely manner. Finally, study materials are sent with tracking in both directions, higher declared value, fragile shipping labels, and a direct signature requirement, to minimize the possibility of being lost, damaged, or delivered to an incorrect address.

Figure 3. Study materials mailed to the participants. CGM: continuous glucose monitor.



Training Call

This call takes place after a participant receives their mailed study materials, using videoconferencing (preferred) or over the phone. The primary purpose of this call is to train participants in use of the study devices. We made efforts to make all the training procedures feasible using only the study phone because not all of our participants have reliable internet access or personal devices to use for videoconferencing (eg, home computer or tablet). Thus, we loaded the necessary videoconferencing software on the study phones and purchased carrier plans providing internet access.

At the beginning of the training call, research coordinators instruct participants on how to self-apply the CGM sensors. This is done first to facilitate checking whether the sensor is operational and recording blood glucose data (which begins after a 1-hour "warm-up" period) before concluding the call. Next, research coordinators guide participants through a participant manual that addresses proper use of all study devices (ie, CGM, accelerometer, study phone), describes the sequence of study events, and explains logistics such as how to mail back the study equipment. Following review of the manual, coordinators guide participants in directed practice with the study phones. To facilitate training over videoconference, participants use the "screen share" feature on the study phone, thereby allowing coordinators to see the participant's phone screen and to provide instructions accordingly. Participants complete directed practice of all study assessments, during which research coordinators explain each question and response choice to ensure the participant's understanding, with the phone in "training" mode (in which survey responses are not recorded as study data).

Once the hands-on phone training is completed, usually enough time has elapsed to allow coordinators to check if the CGM is appropriately recording data. If participants are willing to share their insulin pump data, they are asked to prepare the data to be shared at the follow-up visit. If it becomes apparent to research coordinators throughout the training call process that the participant may not have the prerequisite technical skills, cognitive ability, visual acuity, or manual dexterity for successful completion of study procedures, the participant is discontinued from the study.

Data Collection

Over the 14 days following the training call, participants complete 5-6 EMA surveys per day at 3-hour intervals over 15 hours (eg, 7 AM-10 PM). The survey schedule is personalized to each participant's usual weekday and weekend wake and sleep times. If participants have schedules that do not allow for completion of 6 surveys per day, the schedule is adjusted to 5 surveys per day. Participants receive daily text messages providing feedback regarding the previous day's survey completion and are encouraged to contact the study team whenever any issues occur. Check-in calls, texts, or emails (per

participant preference) are conducted at 1, 4, and 8 days after the training call to help ensure continued CGM and accelerometer wear, troubleshoot any technical issues, and encourage completion of surveys. Participants are also encouraged to contact the study team if any issues occur (eg, EMA survey difficulties, CGM falls off).

Follow-up Call

A follow-up call is scheduled at the conclusion of the 14 days of data collection. During this call, participants are asked to complete follow-up surveys, answer questions regarding the quality of their experience in using the devices and any unusual events over the 14-day period, and are instructed in how to repackage the study equipment to mail back to the study team with a prepaid return label to return study devices. To minimize burden, we provide the option to schedule a package pick-up from the participants' homes or other locations.

Receiving Returned Equipment

To fully close out a participant, a few steps are taken once the equipment is received. First, all the contents of the package are disinfected in accordance with Centers for Disease Control and Prevention guidelines. Afterwards, contents are checked to make note of any missing equipment. Next, data are downloaded from all the study devices and uploaded to the server, and data loss due to technical issues are noted and communicated to the study team. If we find from the CGM data that a participant spent an excessive amount of time in hypoglycemia (below 54 mg/dL >10% of the time), an alert is triggered and personnel notifies the participant as well as his/her diabetes care provider. When all the study equipment is returned, the participant is provided the final US $75 of the stipend. Additionally, participants receive a thank you letter with a copy of their 2-week CGM report via mail or email if it was requested.

Study Measures

Global Measures

Participants completed 2 survey batteries—one at baseline prior to mailing the study materials (Table 1) and one immediately following the EMA data collection period (Table 2). Participants can elect to complete these surveys on their own or with assistance from a research coordinator, and objective demographic and clinical data are confirmed via medical chart review. Surveys were divided into 2 administration periods to reduce testing burden and because some surveys were intended to reference the period of EMA data collection and thus are administered at follow-up. The purpose of the global measures are to (1) characterize the study population; (2) examine how short-term relationships among blood glucose levels, functions, and well-being differ between patients based on their global demographic and clinical characteristics; and (3) investigate how individual differences in these short-term relationships are related to the global well-being and functioning measures. Overall, in selecting global measures, we prioritized breadth over depth. Although the assessment battery is lengthy, we aimed for parsimony when possible, selecting the shortest validated measure for each construct to maximize the number of assessments that could reasonably be included without inducing undue participant burden.

Table 1. Baseline global measures.

Construct	Assessment	Description
Background variables		
N/A[a]	Demographic questionnaire	Gender, ethnicity, education, income, health care coverage, marital status, employment status
N/A	Clinical information	Recent severe high/low blood glucose events, method of insulin delivery, pump/injections/continuous glucose monitor use, diagnoses, height and weight
Personality	10-item personality inventory [17]	10 items, measures personality along 5 dimensions
Diabetes management		
Self-management	Diabetes self-management questionnaire [18]	16 items, higher scores indicate more desirable self-management behavior
Insulin self-management	Insulin self-management	3 items, inspired by medication adherence items [19], also administered at follow-up
Diabetes self-care	Self-Care Inventory-Revised [20]	9 items, higher scores signal increased levels of diabetes self-care, 4 subscales
Emotional well-being		
Fear of hypoglycemia	Hypoglycemic attitudes and behavior scale [21]	14 items, higher scores indicate more fear of hypoglycemia
Anxiety	Generalized Anxiety Disorder Assessment [22]	7 items, higher scores indicate increased severity of anxiety
Diabetes stigma	Type 1 Diabetes Stigma Assessment Scale [23]	8 items, higher scores indicate more diabetes stigma experienced, 3 subscales
Emotional regulation	Difficulties in emotion regulation scale [24]	18 items, higher scores reflect greater difficulty with emotion regulation
Depressive symptoms	Patient health questionnaire [25]	8 items, higher scores reflect greater depression symptoms severity
Other		
Occupational balance	Occupational balance questionnaire [26]	11 items, higher scores indicate a higher level of lifestyle balance
Social support	Social support questionnaire [27]	12 items, higher scores signal greater satisfaction with social support system

[a]N/A: not applicable.

Table 2. Follow-up global measures.

Construct	Assessment	Description
Function		
Functional health status	RAND 36-item short form health survey v1.0 [28]	36 items, measures 8 dimensions of health, higher scores indicate better functional health status
Illness intrusiveness	Adapted illness intrusiveness rating scale [29]	13 items, higher scores reflect greater interference associated with the disease (diabetes) and its treatment
Emotional well-being		
Diabetes-related quality of life	Helmsley quality of life and diabetes survey [30]	27-36 items depending on age group, higher scores reflect better diabetes-related quality of life
Diabetes distress	Problem areas in diabetes scale [31]	5 items, higher scores suggest greater diabetes-related emotional distress
Positive and negative affect	Stress and Working Memory Study Affect Items [32]	9 items, sum of 4 items indicates positive affect and sum of other 4 items indicates negative affect; 1 item not from original (“tension”) was added
Perceived stress	Perceived stress scale [33]	10 items, higher scores indicate greater perceived stress
Life satisfaction	Satisfaction with life scale [34]	5 items, higher scores reflect greater life satisfaction
Other		
N/A[a]	COVID-19 questions	Provides information about COVID-19 era life circumstances such as economic and lifestyle changes
N/A	Study-specific follow-up questions	Difficulties with the study devices, experience of diabetic ketoacidosis or hypoglycemia during study visit

[a]N/A: not applicable.

Our global assessment battery was adapted to fit the needs of remote research during the COVID-19 pandemic. We dropped 3 planned measures that were not critical to accomplish the study’s aims owing to logistical challenges. One change was eliminating the measurement of HbA_{1c} levels, which capture average blood glucose levels over an approximately 12-week period; the team instead recorded HbA_{1c} readings from the previous 12 months from medical charts, when available, to gain insight into participants’ overall glycemic control as a potential moderator of observed relationships. Additionally, measurements of height, weight, and neck circumference (to assess sleep apnea risk) were dropped, with height and weight now being assessed through self-report. We also removed the National Institutes of Health (NIH) Toolbox cognitive tests [35], which are completed with an in-person test administrator using iPads. Their purpose was to help validate the mobile cognitive assessments being used, but as some validation data already exist for the mobile cognitive assessments, these tests were determined not to be critical. Finally, we added a COVID-19 questionnaire adapted from prior COVID-19 surveys [36,37] to capture the impact of COVID-19–related life changes and help us understand how our study population may be unique as compared to studies conducted before or after COVID-19.

EMA Measures

The EMA questions are outlined in brief in Textbox 2. Multimedia Appendix 1 lists the actual items and response options used. EMA data collection is administered using the mobile EMA (Ilumivu) platform; an HIPAA-compliant EMA system, which incorporates a native smartphone app; a web interface for survey design and deployment; and a secure cloud-based server for data management [38].

Textbox 2. Ecological momentary assessment survey questions.

Morning questions

Domains: sleep quality, sleep/wake time, anticipated busyness, diabetes self-efficacy

Questions are only asked in the first survey of every day

Activity engagement (in all surveys)

Domains: activity type, activity location, activity social situation, activity performance, activity satisfaction, activity importance, diabetes intrusiveness

Questions about activity performance, satisfaction, and importance were derived from the Canadian Occupational Performance Measure [39]

Question about diabetes interference derived from Adapted Illness Intrusiveness Rating Scale [29]

Emotional well-being (in all surveys)

Domains: mood, stress, diabetes distress, fatigue, pain

Mood question formatting was derived from the Positive and Negative Affect Schedule [40], and actual items were from the Stress and Working Memory [32]

Blood glucose (some parts in all surveys)

Domains: Meal intake (yes/no), meals time, insulin intake (yes/no), insulin time, perception of blood glucose

Items derived from a prior diabetes ecological momentary assessment study [41]

Questions referencing the last 3 hours are asked in all surveys except the first survey of every day

Evening questions

Domains: activity performance, insulin self-management, diabetes self-management, study devices statuses, unexpected events, perceived daily demands

Daily demand questions were adapted from the National Aeronautics and Space Administration–Task Load Index [42]

Questions asked in last ecological momentary assessment survey of every day

Momentary Surveys

Survey questions were selected on the basis of being derived from validated global measures or having been used successfully in previous EMA studies [29,39,41-45]. Participants answer approximately 30 survey items in the first 5 surveys of the day and 50 items in the evening survey (depending on branching logic).

Ambulatory Cognitive Assessments

Cognitive performance is assessed with 2 tests taken 6 times daily on the study phone. A “Go/No-Go” task assesses inhibitory control [46] and consists of 75 trials that take approximately 1 minute. Participants are presented a series of images that are either mountains or cities. They are asked to press a button when they see an image of a city but refrain from pressing the button if images of mountains are presented. A “Symbol Search” task assesses visual-spatial attention and processing speed [47] and consists of 20 trials that take approximately 45 seconds. Participants are presented with 2 cards at the top of the screen and 2 at the bottom. They are asked to choose a card from the bottom of the screen that matches one of the cards from the top. Cognitive tests administered through phones have been found to be valid as evidenced by demonstrating expected associations with measures of cognitive testing delivered through in-lab assessments [47]. Retest gains (training effects) are common when cognitive tests are repeated multiple times. Participants in this study undergo careful training of the study procedures and complete the cognitive tests for the first time as part of the training session, and these scores do not enter the analyses. Even though our test stimuli are unchanged across assessments, this may mitigate retest effects to some extent. To evaluate the robustness of results to potential retest gains, we will conduct sensitivity analyses in which the first few cognitive scores are removed from the analyses, and we will examine detrended cognitive scores where individual trends in test scores due to retest effects (eg, exponential decay of response times) are statistically removed from the data.

Study Devices

One of our primary study devices is Abbott’s Freestyle Libre Pro Flash Glucose Monitoring System CGM. To ensure consistency, all participants wear this CGM, regardless of whether they also wear a personal CGM. After initial placement on the back of the upper portion of the participants’ arms, it automatically records glucose levels from interstitial fluid (which is converted via an algorithm to estimate the blood glucose levels) at 15-minute intervals continuously for 2 weeks. CGM data are processed by Abbott using the Freestyle Libre2 Flash Glucose Monitoring System algorithm that meets integrated CGM performance requirements because this algorithm is not yet integrated in the Libre Pro CGM.

The Actigraph wGT3X_BT wrist accelerometer was another core study device. It provides continuous data that can be used to infer time spent in sedentary, light, moderate, vigorous physical activity, and sleep each day [48]. To better account for possible errors in sleep measurement with the Actigraph alone, sleep/wake times are calculated using both Actigraph data and self-reports of sleep/wake times through a weighted average approach as recommended in prior research [49].

Finally, the study phones used were Xiaomi Mi A1 models with Android operating systems. They were chosen because they were relatively inexpensive, had sufficient processing power and screen size to run the cognitive tests, and because the Android operating system was preferred by EMA and cognitive testing programmers. Participants were given study phones rather than using their own devices primarily to ensure the comparability of cognitive testing results. If participants used their own devices, there was a possibility that factors such as differences in the phone processing speed or screen size could affect the cognitive testing scores.

Analytic Plan

Standard statistical diagnosis and descriptive statistics will be used to evaluate the reasonableness, sparseness, and potential nonnormality of the data. Psychometric properties of EMA multi-item scales (eg, mood) will be investigated, including multilevel factor analysis, to confirm the dimensionality of self-report measures, cross-level invariance, and adequate internal consistency of scale scores in between-person and within-person levels [50,51]. Univariate analyses of temporal patterns will be used for some variables to examine diurnal rhythms and systematic trends over time. We will check for outliers and investigate their potential causes, including technical glitches (eg, surveys being delivered at unanticipated times due to time zone changes) and satisficing (putting minimal effort into survey or responding to finish quickly).

Data analysis will be conducted using Dynamic Structural Equation Modeling (DSEM). This method combines multilevel modeling and time-series analysis into a unified framework, allowing for the analysis of multivariate time series obtained from multiple individuals simultaneously [52-55]. Multilevel modeling is a form of linear regression that accounts for nested data (multiple observations nested in individuals) [56]. Rather than analyzing a time series model separately for each individual, DSEM enables us to examine the magnitude and directionality of dynamic relationships between blood glucose and other measures within individuals, while simultaneously allowing for the analysis of quantitative differences in these relationships across individuals in the same model. Larger sample sizes (N=200 in this study) can compensate for shorter time series [55].

Aim 1 focuses on assessing the within-person relationships between blood glucose measures, function, and emotional well-being. Analyses for this aim will begin by checking for between-person and within-person correlations between blood glucose and functioning/emotional well-being variables to gauge the relative magnitude of within-person versus between-person correlations. Lagged temporal relationships between blood glucose and other momentary variables will be examined with DSEM. For instance, DSEM would allow us to elucidate if negative affect precedes hyperglycemia, hyperglycemia precedes negative affect, or if their relationship is bidirectional within or across days.

In aim 2, possible moderators (eg, sex, race/ethnicity, CGM use) of the observed within-person relationships among blood glucose measures, function, and emotional well-being are assessed. For example, we will investigate whether personal CGM use moderates relationships between blood glucose measures and well-being. Because CGM users likely have much greater awareness of their blood glucose levels, we anticipate that their cognitive evaluation of blood glucose may impact their mood, in addition to any physiological pathways between blood glucose measures and mood. As another example, we will examine whether prolonged nocturnal hypoglycemia moderates relationships between blood glucose levels and momentary cognitive functioning. To test potential moderators, cross-level (person-by-situation) interactions will be examined using traditional multilevel modeling and (for more complex models involving moderators of effects in multivariate analyses) DSEM.

For aim 3, we investigate how individual differences in momentary (within-person) associations between blood glucose levels and functioning/well-being relate to global measures of functioning, well-being, and quality of life. For example, patients whose momentary cognitive functioning is more strongly affected by their momentary blood glucose levels may show worse functioning levels overall than patients whose cognitive functioning remains relatively unaffected by fluctuations in their blood glucose levels. If significant effects are found in these analyses, we will also explore the possibility that individual differences in the dynamic relationships between blood glucose and other momentary measures *mediate* the relationships between demographic/clinical characteristics and global measures of functioning and well-being. A hypothetical example would be that men and women differ in how momentary blood glucose affects their momentary mood and that this in turn explains gender differences in the overall mental well-being. DSEM methods will again be used here, where global functioning measures will serve as dependent variables, and random effects (ie, latent individual differences) of the short-term (within-person) dynamics will serve as independent variables or as intermediate variables (in potential mediator models) [53].

Prior to collecting and analyzing the full data set, we are investigating simpler subquestions of our overarching aims to help determine how to best model the data. One “simple” question, for instance, is how high blood glucose levels affect functioning at the within-person level (aim 1). This seemingly innocuous question brings with it a host of other queries: *What parameters of a high blood glucose level need to be considered (eg, time with high blood glucose levels, time since high blood glucose levels were detected, magnitude of high blood glucose levels)?* and *What variables best capture functioning: self-report or objective cognitive measures?* Another subquestion is how nighttime blood glucose affects functioning the next day, which requires consideration of *How should night-time blood glucose be summarized (eg, average blood glucose levels, time in range, coefficient of variation, etc?)* and *How can we delineate the time sleeping given our available data?* As we tackle these subquestions, we will gradually increase our understanding of the data and the best fitting models to be better prepared to conduct more robust analyses when the full data set is collected. This process is necessary, given the novelty of analyzing within-person momentary relationships among blood glucose levels, functioning, and emotion.

Sample Size and Power Considerations

We designed the study to have at least 80% power for the detection of the anticipated effect sizes of .10 (3% of the variance) to .25 (6% of the variance), corresponding with small to medium effects. Power calculations were conducted using Monte Carlo simulations, assuming a ratio of random intercept to within-person residual variance of 1.5/1, a ratio of random intercept to random slope variance of 5/1, a first-order autocorrelation of 0.4, and 80% compliance with EMA (based on our prior research). A sample size of 200 patients observed 6 times/day over 14 days will provide 80% power (α=.01, adjusted for multiple comparisons) to detect an effect size of .10 for lagged within-person relationships (aim 1), an effect size of .18 for cross-level interactions (moderators of within-person relationships, aim 2), and an effect size of .23 for random effects of within-person relationships as predictors of between-person outcomes (aim 3).

Results

Since initiating data collection in June 2020, our goal has been to recruit approximately 11 participants per month to attain our targeted sample size of 200 participants within 18 months. Following 12 months of recruitment, 124 participants have successfully enrolled in the FEEL-T1D study (excluding 4 patients who did not complete baseline assessment), and we project to complete enrollment by November 2021 (Table 3). Overall, remote study implementation has been a success. Weekly meetings are held to discuss study implementation issues that arise, and team members who are experts on various aspects of data collection are consulted as needed. The details of the study implementation to date are given in Table 3.

Table 3. Study implementation statistics (as of May 31, 2021).

Statistics	All sites, n (%)	Westside Center for Diabetes, n (%)	Los Angeles Roybal Clinic, n (%)	Einstein College of Medicine/Montefiore Medical Center, n (%)
Participants enrolled	124 (100.0)	37 (29.8)	36 (29.0)	51 (41.1)
Participants withdrew	5 (4.0)	3 (8.1)	2 (5.5)	0 (0.0)
Participants in progress	19 (15.3)	5 (13.5)	9 (25.0)	5 (9.8)
Participants completed	100 (80.6)	29 (78.4)	25 (69.4)	46 (90.2)
Data quality: number of days with concurrent ecological momentary assessment, continuous glucose monitor, and accelerometer data				
10 days or more	82 (82.0)	23 (79)	20 (80)	39 (85)
1-9 days	11 (11.0)	1 (3)	5 (20)	5 (11)
0 days	7 (7.0)	5 (17)	0 (0)	2 (4)

Overall, adherence and data quality have been very good thus far (Table 4). The EMA survey compliance rate has been consistently high (7082/8087, 87.6% of all prompts) as has completion of ambulatory cognitive assessments (6795/8087, 84.0% compliance). Of the 100 participants who completed the study at the time of this report, 82 participants provided concurrent CGM, EMA, and accelerometer data for at least 10 of the 14 days of data collection. Of those who did not provide complete data, problems included incomplete (<7 days) or missing CGM data (n=6 and n=5, respectively) and incomplete (<7 days) or missing accelerometer data (n=8 and n=6, respectively), with some participants having missing data from both devices. Five participants who enrolled did not complete the study: reasons included personal/family emergency (n=1), feeling that the study was too burdensome (n=2), and acute health conditions (n=2).

Table 4. Data of survey completion.

Survey completion data	Overall (N=8087)	Morning (n=1400)	Midday (n=5287)	Evening (n=1400)
Surveys completed, n (%)	7082 (87.6)	1232 (88.0)	4629 (87.6)	1221 (87.2)
Duration (min) (excluding cognitive tests), mean (SD)	2.9 (3.1)	3 (2.8)	2.4 (3.1)	4.5 (2.8)

Discussion

FEEL-T1D is, to our knowledge, the first study to examine dynamic reciprocal relationships between blood glucose levels, objective cognitive and physical function, and subjective function and well-being among adults with T1D. It is one of only 3 studies, to our knowledge, using EMA methodology to investigate associations between CGM-derived blood glucose metrics and other momentary variables among individuals with diabetes, with the other 2 being the international HypoRESOLVE (Hypoglycemia Refining Solutions for Better Lives) project [57] and the DIA-LINK study in Germany [58]. This study is innovative in its use of CGM, EMA, mobile cognitive testing, and accelerometry, analyzed with sophisticated statistical methods, to achieve its aims. Knowledge generated from this study will provide actionable insights for researchers, clinicians, and people living with diabetes by facilitating tailoring of diabetes treatments to maximize function and well-being in addition to physical health and by informing the development of interventions that address the dynamic relationships between these constructs. Furthermore, to increase the generalizability of our results, we are recruiting a diverse sample with respect to race, ethnicity, socioeconomic status,

and diabetes treatment approaches. We attribute our success in the study's implementation, to date, to a carefully crafted set of procedures for remote data collection to promote participant adherence to the study protocol, abide by social distancing requirements necessitated by COVID-19, and maintain the quality of data collected.

Fully remote implementation comes with several benefits. Foremost among them is that, owing to restrictions on in-person contact and our ethical obligation to protect study participants from harm, conducting the study during the COVID-19 era *would not have been possible* without remote implementation. When California and New York issued stay-at-home orders in March 2020, with an uncertain future ahead, our choices were to adapt our study procedures or to wait indefinitely until in-person data collection was feasible again. Additionally, remote data collection has also allowed us to enroll participants living far away from study sites. Thus, the creation of a remote protocol has increased recruitment opportunities and potentially diversified our study population. Remote data collection has also freed us from logistical challenges related to in-person data collection, such as ensuring that participants have access to parking and transportation when visiting study sites. Relatedly, scheduling study appointments has been much easier because participants can complete them at home instead of having to factor in transportation costs and time. Finally, remote data collection has given us the option to more neatly enact division of labor, thereby enabling team members to specialize and perform study procedures more efficiently. Some team members specialize in recruitment and participant contacts, while others focus on preparing and shipping data collection kits or processing data. In our previously planned in-person arrangement, each research coordinator was responsible for a wide range of tasks, including walking participants through data collection, setting up devices to be loaned to participants, and downloading data from devices when returned. Because of the logistical complexity of the various tasks, allowing team members to specialize has been more efficient.

Despite its benefits, the transition to remote data collection has also had some drawbacks. We were unable to use some of the measures we had initially planned on administering, such as the NIH toolbox and point-of-care HbA_{1c}, and therefore cannot compare our mobile cognitive testing and continuous blood glucose data to their more traditional counterparts. Another drawback has been the additional requirement for our research coordinators and study participants to be adept in using videoconferencing software. Because our less technologically savvy participants are disproportionately older or live in areas with poor internet connectivity, the generalizability of our study results among these populations may be limited. In addition, inherent in fully remote study procedures has been a greater frequency of technical and mailing issues. Unexpected software updates have caused videoconferencing not to work, and internet connection issues have led to the postponement of scheduled video calls. Unforeseen mailing delays have led to delays in study appointments, and misplaced packages require extra effort to track down. Finally, shipping and processing our data collection equipment is costly and has required significant personnel time.

Assuming that the effects of COVID-19 will continue over the duration of our data collection, we will not have a way to compare COVID-19 and non-COVID-19 pandemic participants. With data gathered from the FEEL-T1D COVID-19 questionnaire that addresses life changes as a result of the pandemic, we may be able to provide descriptive data characterizing our sample and thereby allowing basic comparison to "normal" participants. Questions asked include "Compared to before the coronavirus outbreak, how would you now describe your current overall level of stress or worry?" and "Have you experienced any of the following major life changes related to the coronavirus outbreak?" (eg, laid off or furloughed, having children at home who usually attend school, camp, or daycare, and major change in the health of a family member).

In summary, the FEEL-T1D study aims to fill gaps in the knowledge about the relationships between short-term blood glucose levels and both momentary functioning and well-being. Our efforts to launch the study were delayed by the COVID-19 pandemic, but we were able to reconfigure our data collection protocol to be fully remote. With our reconfigured procedures, we have successfully recruited participants and have high completion rates over 2 weeks of nontrivial data collection, in spite of the challenges of conducting research with social distancing requirements in effect. We anticipate that the data provided by the FEEL-T1D study will answer questions of importance to the T1D community regarding optimal glycemic patterns for mood changes and functional ability and facilitate individualized tailoring of treatments to maximize the well-being and quality of life of persons with T1D.

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Authors' Contributions

EAP, SS, AP, VR, JC, HJ, JSG, and DSM contributed to the conception or design of the work; RH, LP, KM, VR, CJH, GCR, HMR, MH, and MW contributed to the acquisition of data; EP, SS, AP, JC, PJL, JSG, and DSM contributed to the analysis and

interpretation of the work; EP, RH, LP, and KM drafted the work; SS, AP, VR, JC, PJL, HJ, CJH, GCR, HR, MH, MW, SSD, JSG, and DSM revised the work critically for important intellectual content.

Conflicts of Interest

AP serves on the Advisory Board at Abbott Diabetes Care and received donated devices from Abbott for research purposes. The funder did not contribute to the design, analysis, or interpretation of the study results.

Multimedia Appendix 1
Full ecological momentary assessment survey battery.
[DOCX File , 17 KB - resprot_v10i10e30901_app1.docx]

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Abbreviations

CGM: continuous glucose monitor
DSEM: dynamic structural equation modeling
EMA: ecological momentary assessment
FEEL-T1D: Function and Emotion in Everyday Life with Type 1 Diabetes

HbA_{1c}: hemoglobin A_{1c}
HIPAA: Health Insurance Portability and Accountability Act
NIH: National Institutes of Health
REDCap: research electronic data capture
T1D: type 1 diabetes

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Protocol

Assessing a Smartphone App (AICaries) That Uses Artificial Intelligence to Detect Dental Caries in Children and Provides Interactive Oral Health Education: Protocol for a Design and Usability Testing Study

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Abstract

Background: Early childhood caries (ECC) is the most common chronic childhood disease, with nearly 1.8 billion new cases per year worldwide. ECC afflicts approximately 55% of low-income and minority US preschool children, resulting in harmful short- and long-term effects on health and quality of life. Clinical evidence shows that caries is reversible if detected and addressed in its early stages. However, many low-income US children often have poor access to pediatric dental services. In this underserved group, dental caries is often diagnosed at a late stage when extensive restorative treatment is needed. With more than 85% of lower-income Americans owning a smartphone, mobile health tools such as smartphone apps hold promise in achieving patient-driven early detection and risk control of ECC.

Objective: This study aims to use a community-based participatory research strategy to refine and test the usability of an artificial intelligence–powered smartphone app, AICaries, to be used by children's parents/caregivers for dental caries detection in their children.

Methods: Our previous work has led to the prototype of AICaries, which offers artificial intelligence–powered caries detection using photos of children's teeth taken by the parents' smartphones, interactive caries risk assessment, and personalized education on reducing children's ECC risk. This AICaries study will use a two-step qualitative study design to assess the feedback and usability of the app component and app flow, and whether parents can take photos of children's teeth on their own. Specifically, in step 1, we will conduct individual usability tests among 10 pairs of end users (parents with young children) to facilitate app module modification and fine-tuning using think aloud and instant data analysis strategies. In step 2, we will conduct unmoderated field testing for app feasibility and acceptability among 32 pairs of parents with their young children to assess the usability and acceptability of AICaries, including assessing the number/quality of teeth images taken by the parents for their children and parents' satisfaction.

Results: The study is funded by the National Institute of Dental and Craniofacial Research, United States. This study received institutional review board approval and launched in August 2021. Data collection and analysis are expected to conclude by March 2022 and June 2022, respectively.

Conclusions: Using AICaries, parents can use their regular smartphones to take photos of their children's teeth and detect ECC aided by AICaries so that they can actively seek treatment for their children at an early and reversible stage of ECC. Using AICaries, parents can also obtain essential knowledge on reducing their children's caries risk. Data from this study will support a future clinical trial that evaluates the real-world impact of using this smartphone app on early detection and prevention of ECC among low-income children.

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KEYWORDS

artificial intelligence; smartphone app; mDentistry; dental caries; underserved population; mobile dentistry

Introduction

Early childhood caries (ECC) is by far the most common chronic childhood disease, with nearly 1.8 billion new cases per year worldwide [1-3]. In the United States, it afflicts approximately 37% of all children aged 2-5 years but disproportionately affects up to 55% of low-income and minority children. Untreated ECC often leads to higher risk of caries lesions in permanent teeth, diminished oral health–related quality of life, hospitalizations and emergency room visits due to systemic infection, and even death [4,5]. Hence, more innovative/effective preventive and treatment strategies are needed, particularly early detection of ECC.

The current biomedical approach to control the ECC pandemic has had limited success. Primarily, this approach focuses on individual-level restorative procedures rather than populationwide preventive strategies. Dental caries is localized destruction of dental hard tissues (enamel and dentin) by acidic by-products from the microbial fermentation of carbohydrates. In the early (subclinical) stages, such as white spot lesions on the tooth enamel surface, caries can be reversed. Many US preschool children from low-income families, however, often have poor access to pediatric dental services; limited dental access leave the underserved children in positions where dental caries is often diagnosed in later stages, thus requiring more extensive restorative treatments. Moreover, ECC is a multifactorial disease with host, microorganisms, diet, and oral hygiene practices as the factors that determine the risks [6-9]. Children's parents/caregivers need to be engaged around these risk factors and acquire skills to self-manage risk to reduce children's risk for ECC.

To combat this ECC pandemic and overcome the barriers of lacking dental access among underserved children and lacking self-management awareness of these children's caregivers, our long-term goal is to develop a first-of-its-kind artificial intelligence (AI)–powered smartphone app to be used by children's parents, which offers patient-centered caries detection and caries risk management.

Smartphone apps have been successfully applied in managing individual behaviors and health conditions [10] such as smoking cessation, weight loss, medication adherence, and Parkinson disease progression monitoring [10-12]. With 77% of all age American individuals [13] and more than 85% of lower-income mid-age American individuals [14,15] owning a smartphone, a smartphone app presents as a suitable and innovative way of providing oral health interventions. Recently, mobile dentistry has been brought up by researchers to promote oral health care at a broad population base [16,17]; however, current oral health smartphone apps are limited in scope and audience. First, compared to the large amount of available medical health apps in the commercial app store, the number of apps that are oral health focused is minimal. Second, most of the available apps are designed for improving the efficiency of tooth brushing or helping users understand oral disease types and manifestation. There is no technology, much less any app, that can be used by parents for early detection of caries in their children. Furthermore, using AI to aid imaging recognition has been applied to improve disease diagnosis in many medical fields including oncology, ophthalmology, radiology, etc [18-21]. However, modern dentistry has not used AI imaging technology for caries detection. To our knowledge, AICaries will be the first app using this technology in dentistry.

In summary, a patient-friendly smartphone app coupled with AI-powered caries detection holds promise in facilitating early clinical confirmation and treatment of ECC. Led by experts in AI imaging recognition, oral health, and mobile health (mHealth), this AICaries study will address the gap in research and clinical practice for ECC from the angle of disease early detection and self-management using mHealth tools.

Methods

Aims

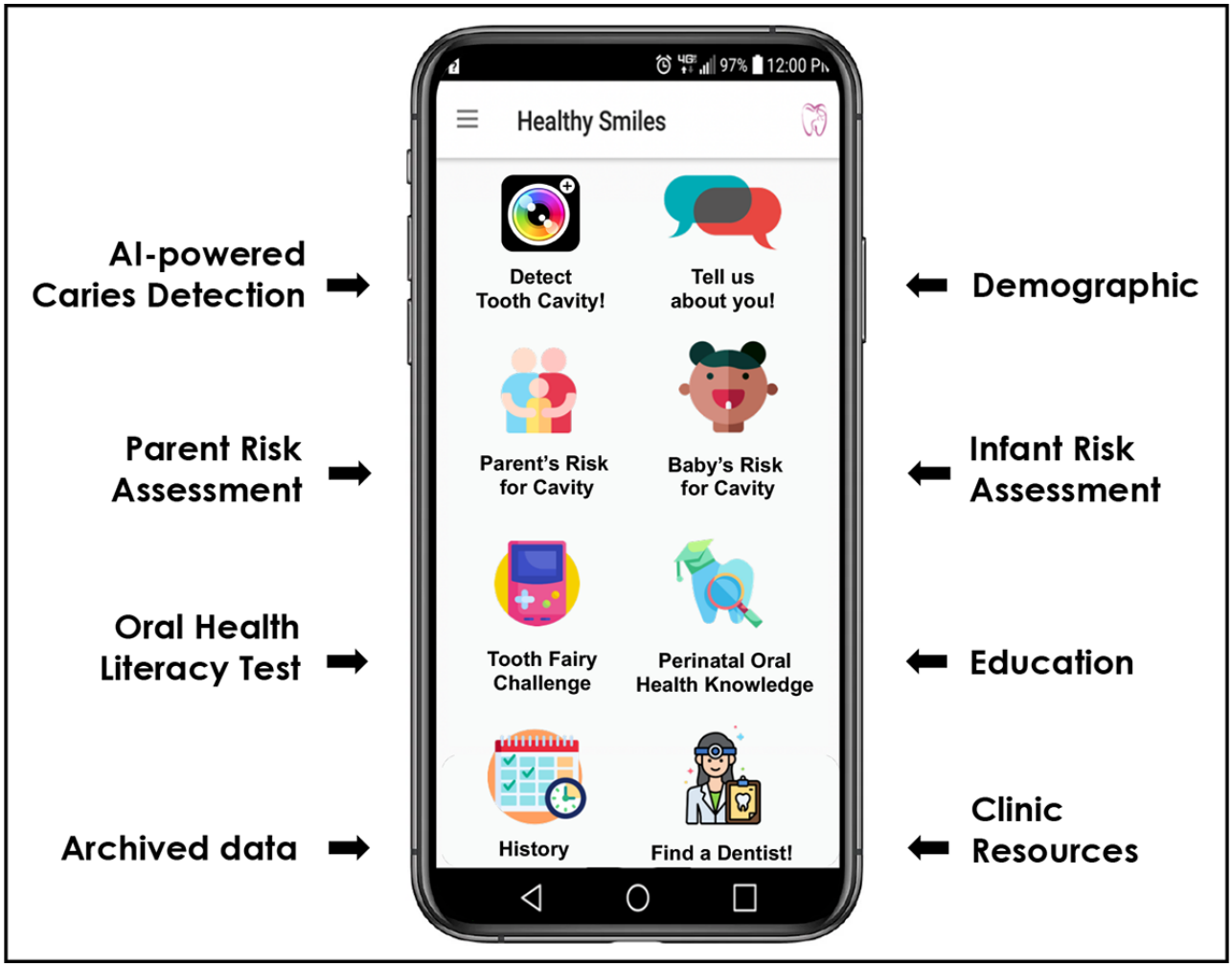
The purpose of the study is to use a community-based participatory research strategy to refine and test the usability of an AI-powered smartphone app, AICaries, to be used by children's parents/caregivers for dental caries detection in their children.

Overall Study Design

Phase I: Refine the AICaries App

We used an integrate, design, assess, and share framework [22] and developed a smartphone app prototype (AICaries) to be used by children's parents. The app shell includes the content shown in Figure 1. Although some components of the app are to be used specifically by mothers, the components that are related to the children could be used by both mothers and fathers of the children.

Figure 1. Components of AICaries smartphone app. The AICaries app prototype houses the AICaries tool for caries detection and other developed app components including maternal and child's caries risk assessment, and education and clinic resources. AI: artificial intelligence.



- AI-powered caries detection algorithm: our team has archived a data set with more than 100,000 high-quality intraoral photos including front and posterior teeth. Using a semiauto dental caries annotation software developed in house, trained and calibrated dentists have annotated approximately 40,000 individual tooth photos for dental caries using the International Caries Diagnosis System [23,24] visual diagnostic criteria as the reference for caries detection and severity scoring. These annotated tooth images were used for developing the AI-powered caries detection algorithm. The performance of the AICaries caries detection algorithm will be assessed in a separate study.
- Maternal risk assessment and child risk assessment: an interactive caries risk assessment tool for mothers and young children. We modified the elements in the American Dental Association (ADA) Caries Risk Assessment system for less health-literate individuals. Through these assessments, mothers can visualize how daily oral hygiene behavior and diet could impact their and their children's caries risk.
- Validated perinatal oral health literacy index: to measure mother's oral health literacy [25,26]
- Maternal and children's oral health education resources: we assembled a series of informative educational materials that provide appropriately timed information specific to pregnant women's oral health importance, children's tooth development, children's oral hygiene, and diet recommendations.
- List of available dental clinics that accept dental insurance for low-income groups (eg, Medicaid): built upon the list developed by the University of Rochester Eastman Institute for Oral Health (EIOH) and our community partner Healthy Baby Network via a New York State Department of Health grant "MICHC Oral Health Manual and Toolkit"

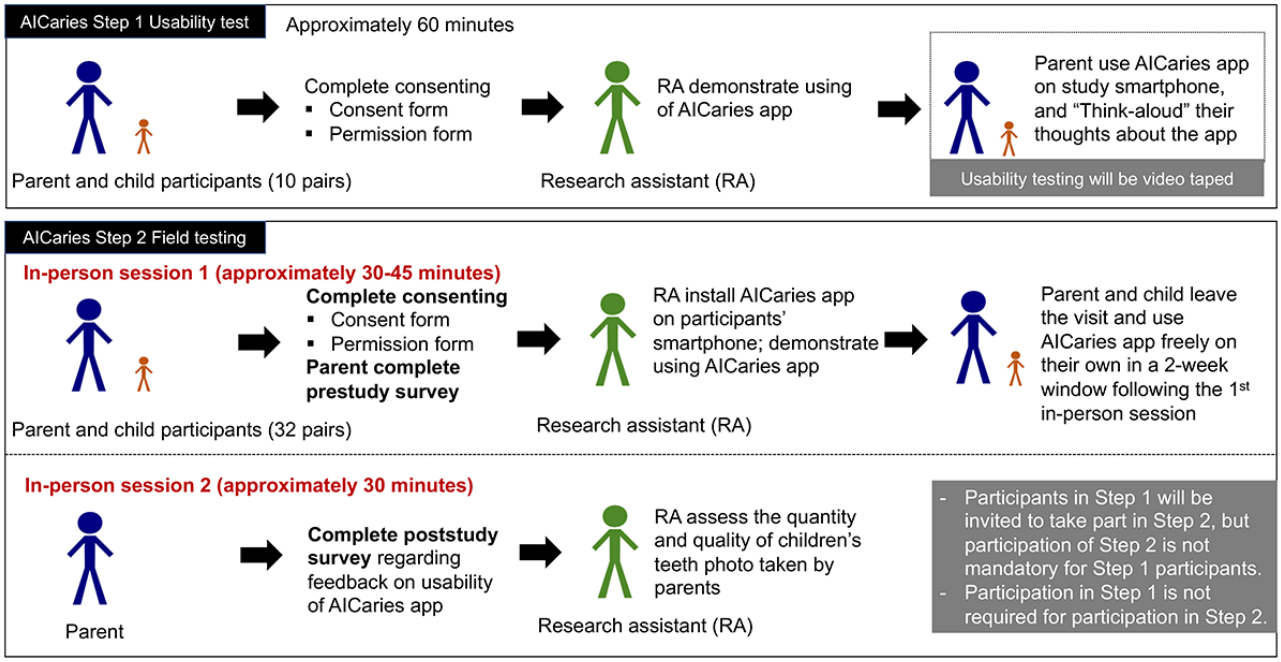
The AICaries app prototype houses the AICaries tool for caries detection and other developed app components including maternal and child's caries risk assessment, and education and clinic resources.

Phase II: Usability Testing

This AICaries study will use the qualitative study design to assess the feedback and usability of the app component, app flow, and whether parents can take photo of children's teeth on their own. The proposed human study will not assess the AI performance, which will be assessed in a separate study.

Specifically, we will conduct iterative moderated usability testing and refinement for the AICaries app that was developed and will be refined by our study team. Briefly, we will conduct the study in 2 steps, detailed in Figure 2.

Figure 2. AICaries usability test study flow.



- Step 1 AICaries usability test: we will conduct individual usability tests among 10 pairs of end users (parents with young children: 10 parents and 10 children) to facilitate app module modification and fine-tuning using think-aloud and instant data analysis strategies. Only one study session was designed.
- Step 2 AICaries field testing: we will conduct unmoderated field testing for app feasibility and acceptability. Field testing will be conducted in the real world among 32 pairs of parents with their young children (a total of 64 participants: 32 parents and 32 children younger than 5 years) to assess the usability and acceptability of AICaries, including assessing the number/quality of teeth images taken by the parents for their children and parents' satisfaction. Two study sessions are designed (detailed in the section Study Procedures).

Participants

A total of up to 84 participants, 42 parents and 42 children younger than 5 years of age will be enrolled in the study. The study population will consist primarily of economically and socially disadvantaged parents 18 years and older (mainly mothers) and their young children (<5 years of age). We expect the participants to be 40% White, 45% Black or African American, 5% Asian, and 10% other race; we expect the composition of ethnical groups among the study sample is 80% non-Hispanic and 20% Hispanic. Since mothers are the primary caregiver for children, the ratio between female and male of the parent participants is expected to be 4:1, with 80% mothers and 20% fathers. Both male and female children will be recruited. Detailed inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Parents who have young children

- Inclusion criteria
  - Provide signed and dated informed consent
  - Have an Android smartphone that could be installed with the AICaries app
  - Willing to comply with all study procedures and be available for the duration of the study
  - Female or male, 18 years or older
  - Have at least 1 child aged between 1-5 years
  - Eligible for state-supported Medicaid type of insurance (eg, Medicaid, Blue Choice, MVP Option, Fidelis Medicaid; note, we are using the insurance eligibility to select low-income participants)
  - English speaking
- Exclusion criteria
  - Participants who have decisional impairment and are incapable of making an informed decision about their participation in the study

Preschool children

- Inclusion criteria
  - Female or male, aged between 1-5 years
  - Eligible for state-supported Medicaid type of insurance (eg, Medicaid, Blue Choice, MVP Option, Fidelis Medicaid)
- Exclusion criteria
  - Orofacial deformity (cleft lip, cleft palate, oral-pharyngeal mass)
  - Down syndrome or other developmental disabilities

Recruitment

We will conduct face-to-face recruitment at the following two sites. The characteristics of these clinics make them suitable for the recruitment in the proposed study.

1. University of Rochester Medical Center (URMC)–EIOH Perinatal Dental Clinic: the URMC-EIOH Perinatal dental clinic was founded in March 2018 and is dedicated to serving socioeconomically disadvantaged pregnant women, women post partum, and young children. Since its founding, URMC-EIOH Perinatal Dental Clinic has provided dental care to more than 300 mothers and their children. A majority of the patients at the EIOH Perinatal Dental Clinic are eligible for state-supported Medicaid type of insurance, which is one of the eligibility requirements of the study.
2. URMC, Highland Family Medicine (HFM): URMC-HFM is one of the largest family medicine residency teaching practices in Monroe County, New York. HFM provides comprehensive prenatal care to the mothers and care to the baby from birth through childhood. Medical records showed that more than 600 children younger than 5 years (44% African American, 39% Caucasian, 7% Asian, and 10% other) are seen at HFM each year.

Retention Strategies

The AICaries step 2 field testing involves 2 in-person study sessions. The research assistant (RA) will phone or text to remind participants about the upcoming study visits approximately 3 days prior to the session. We will try to accommodate their social, economic, or physical barriers to coming for a study session, such as providing transportation and parking assistance.

Study Procedures

Step 1 AICaries Usability Test

We will conduct 10 in-person, one-on-one, 60-minute usability tests of the smartphone to facilitate app module modification and fine-tuning using think-aloud [27] and instant data analysis strategies [27].

- The parent will be asked to bring one child with them to the study site (URMC-EIOH), involving a quiet room equipped with Wi-Fi and videotaping, staffed by two trained RAs.
- Following informed consent, the RA who is moderating will ask the parent to complete a brief survey (part 1 of Multimedia Appendix 1) that includes the age of the parent and child, parent's sex, educational level, frequency of use of smartphone apps, and use of phone for photographs. The second RA will monitor the child.
- Prior to the testing, one RA will briefly demonstrate how to use the app and think-aloud strategy to express their feedback while testing the app.
- The parent will then use the app while thinking aloud throughout the entire process.
- The key usability tasks include navigation of the app interface; accessing and completing the ADA caries risk

assessment; and, notably, taking usable (diagnostic) photographs of their child's front teeth using the photo-taking interface.

- The RA will provide encouragement and affirmation throughout, and only offer assistance if the parent hits a clear road block. The RA will provide facilitating statements (eg, "I noticed you did X. Can you explain why?") or echoing comments. At the end of the session, the parent will be asked about suggestions for improvement.
- Each session will be videotaped. The recording will start with participants' verbal permission. We will inform the participants when the recording stops. The videotape will be reviewed by the study team immediately after the session using instant data analysis [27] with attention to photo image quality following assessment criteria in parts 3 and 4 in Multimedia Appendix 1. Each user challenge will be ranked as critical (required assistance to proceed), moderate (major delay or frustration), or cosmetic (minor) and annotated to the exact interface/task. Based on rankings, the team will suggest changes in the instructional video, app design, and study procedures. The changes will be incorporated into subsequent testing sessions.

Step 2 AICaries Field Testing

The unmoderated field testing allows the end users to interact with the AICaries app in their natural environment. We will enroll 32 pairs of parents and their young children, a total of 64 eligible participants, for step 2 of the AICaries study. There are two in-person study sessions.

1. At the first in-person session, approximately 30 to 45 minutes, following informed consent, the participants will complete a baseline questionnaire (part 1 of Multimedia Appendix 1. The RA will then install the AICaries app on participants' smartphone. After the participants complete the first study visit, over the course of the next 2 weeks, they will test the app and take photo images of their child's front teeth only (no facial features) and send them to the study team via SMS text messages. If the participating parent fails to send their child's teeth photo to the study team by the end of 2 weeks, our RA will call or text participating parents to remind them about the study activities.
2. The second in-person study session will take place after the 2-week app testing; the participants will come to the study site, complete a brief in-person survey (part 2 of Multimedia Appendix 1) of Likert items that address ease-of-use of the instructional support quality, ease-of-learning to take correct photographs, and overall satisfaction. App use metrics will include quantity and quality of children's teeth images taken by the parents. The participants will also be interviewed about their experience of using AICaries based on a semistructured interview guide (part 5 of Multimedia Appendix 1). Interview sessions will be audio recorded, transcribed, and analyzed qualitatively for thematic content. Additionally, the RA will debrief with the participant and elicit suggestions for improvement.

Statistical Analysis

Sample Size Considerations

Step 1 AICaries Usability Test

We expect to reach data saturation [28] (no new suggestions are proposed) after conducting 10 individual usability tests. The sample size is determined based on previous published studies, where between 6 to 11 usability tests were conducted to assess smartphone app usability [29,30].

Step 2 AICaries Field Testing

A sample size of 28 produces a two-sided 95% CI with a width equal to 0.3 when 80% of parents produce usable tooth images for their children using AICaries. Considering a dropout rate of 10%, we plan to recruit 32 parents and their children.

Data Analysis

Qualitative Data

The transcribed data for the step 1 AICaries usability test and step 2 AICaries field testing will be coded with predetermined open codes. Thematic content will be further analyzed using categorizing and contextualizing strategies to understand the needed improvement for the AICaries app.

System Usability Scale

For the step 2 AICaries field testing, the System Usability Scale (SUS) will be used to assess the acceptance of the AICaries (part 2 of Multimedia Appendix 1). The SUS instrument [31-33] is widely adopted in business and technology industries and mHealth fields to measure and quantify the perception of product and service usability. A SUS score above 68 indicates above-average usability; a score above 80.3 indicates excellent usability of the AICaries app. Baseline information of the participants that are collected, such as previous use of smartphone apps or taking part in the step 1 study, which might make participants more familiar with the app, will be taken into consideration during the usability analysis. Additional quantitative data that will be analyzed are app use metrics that will include which screens opened, time between screens, and numbers/quality (whether photos could be used for clinical diagnosis for dental caries) of images taken (part 5 of Multimedia Appendix 1).

Results

The study has been peer reviewed and funded by the National Institute of Dental and Craniofacial Research, United States. The research ethics application has been reviewed and approved by the University of Rochester Research Subject Review Board (IRB STUDY00005772, 00003953, 00005949). The AICaries smartphone app usability was launched on August 6, 2021. Data collection and analysis are expected to conclude by March 2022 and June 2022, respectively.

Discussion

Study Innovation

National surveys in the United States have shown that low-income and minority children not only are

disproportionately affected by ECC but also have limited access to oral health care [34,35]. The percentage of US children aged 0-6 years with at least one dental visit is much lower among families whose income are lower than the federal poverty line [34,35]. One way to address this health system dilemma is to make the oral disease screening service accessible to individual patients regardless of their socioeconomic condition, such as via mHealth tools. Currently, patients can monitor their blood pressure via home use blood pressure devices; patients can monitor their blood glucose via home use glucose meter; patients can even monitor their heart rate and rhythm via a smartwatch. In contrast, when monitoring oral health, other than visiting dental professionals, patients have no way to monitor their oral diseases using a personal device. The AICaries smartphone app will be a first-of-its-kind patient-centered caries early detection and screening tool, and a useful resource for caries risk assessment and oral health education.

Implications

Using AICaries, parents can use their regular smartphones to take photos of their children's teeth and detect ECC, aided by AICaries, so that they can actively seek treatment for their children at an early and reversible stage of ECC. Using AICaries, parents can also obtain essential knowledge on reducing their children's caries risk. Data from this study will support a future clinical trial that will evaluate the real-world impact of using this innovative smartphone app on early detection and prevention of ECC among low-income children.

Acknowledgments

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Authors' Contributions

JX, JL, TTW, TD, and KF contributed to the conception; design; data acquisition, analysis, and interpretation; and drafting and critically revising the paper. NAJ, OLM, and SB contributed to data acquisition, analysis, and critically revising the manuscript. All authors have read and approved the final version of the paper and agree to be accountable for all aspects of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data collection and assessment forms.
[DOCX File , 44 KB - resprot_v10i10e32921_app1.docx]

Multimedia Appendix 2
National Institutes of Health grant peer-review summary.
[PDF File (Adobe PDF File), 126 KB - resprot_v10i10e32921_app2.pdf]

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Abbreviations

ADA: American Dental Association
AI: artificial intelligence
ECC: early childhood caries
EIOH: Eastman Institute for Oral Health
HFM: Highland Family Medicine
mHealth: mobile health
RA: research assistant
SUS: System Usability Scale
URMC: University of Rochester Medical Center

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Protocol

Automated Virtual Reality Cognitive Therapy for People With Psychosis: Protocol for a Qualitative Investigation Using Peer Research Methods

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Abstract

Background: Many people with psychosis experience difficulties in everyday social situations. Anxiety can make life challenging, leading to withdrawal. Cognitive therapy, using active in vivo learning, enables people to overcome fears. These treatments are not readily available to people with psychosis. Automated virtual reality (VR) therapy is a potential route to increase accessibility. The gameChange automated VR cognitive therapy is designed to help people overcome anxious avoidance and build confidence in everyday social situations. A virtual coach guides the person through the treatment. Understanding user experience is key to facilitating future implementation. Peer research methods, in which people with lived experience of the issues being studied are involved in collecting and analyzing data, may be useful in developing this understanding. This encourages researchers to draw on their lived experience to explore participant perspectives and co-create knowledge.

Objective: The primary objective is to use a peer research approach to explore the participant experience of a novel automated VR therapy for anxious social avoidance. This includes understanding (1) the experience of anxious social avoidance in people with psychosis, (2) the experience of the gameChange automated VR cognitive therapy, and (3) any potential impact of the therapy in people's lives. This will inform future implementation strategies. The secondary objective is to explore how peer research can be used to co-create knowledge.

Methods: Semistructured interviews will be conducted with approximately 25 people with psychosis participating in the gameChange trial (ISRCTN17308399). Participants will be recruited from the five trial centers based in National Health Service mental health trusts across England. Interviews will be conducted by two researchers. One is a peer researcher with similar lived experience to the trial participants. The other has lived experiences of mental health issues that do not directly overlap with those of the trial participants. Interview questions will focus on an individual's experience of anxious social avoidance, experiences of participating in the gameChange VR therapy, and any changes or impact following therapy. The interview schedule was developed

in collaboration with the gameChange Lived Experience Advisory Panel (LEAP), comprising 10 project advisors with lived experience of psychosis. Interpretative phenomenological analysis and template analysis will be used to explore individual accounts. The LEAP will contribute to the analysis.

Results: Data collection will be conducted from April to September 2021, and analysis will be conducted from June to October 2021. As of September 28, 2021, 20 participants had been interviewed, and coding is underway.

Conclusions: The study, employing a peer research approach, may provide a unique insight into the experiences of anxious social avoidance in people with psychosis and its treatment using automated VR therapy. This will inform potential future implementation of VR automated therapies in mental health services.

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KEYWORDS

virtual reality; therapy; schizophrenia; agoraphobia; peer research; qualitative methods; implementation; mental health; psychosis; cognitive therapy

Introduction

Background

Many people with psychosis withdraw from everyday social situations due to anxiety, leaving them isolated and inactive. In a survey of 1800 people with nonaffective psychosis attending National Health Service (NHS) mental health services, two-thirds had levels of anxious avoidance comparable to agoraphobia [1]. Social avoidance has significant consequences for both mental and physical health. Although anxious avoidance is a common clinical problem, with significant negative consequences, there are no in-depth explorations of first-person accounts of anxious avoidance in people with psychosis.

The anxiety is likely to arise from several sources, such as hearing threatening or critical voices, social anxiety, paranoia, or low self-esteem. These fearful cognitions lead to avoidance or, when this is not possible, the use of in situ defense (or safety-seeking) behaviors, which prevent the receipt and processing of disconfirmatory evidence and thus maintain the anxious thought. Cognitive treatments for anxiety target the fearful cognitions and defense (or safety-seeking) behaviors [2]. Behavioral experiments provide an opportunity to test an individual's anxious cognitions while their defenses are dropped. Overcoming anxious cognitions requires an active approach to re-evaluate fearful cognitions and generate alternative cognitions and responses in the moment. However, fearful beliefs can make this work challenging.

Virtual reality (VR; interactive computer-generated environments) provides a route to test anxious cognitions by entering simulations of feared situations. VR elicits similar cognitive and emotional responses to real-world situations (eg, [3]). However, people are aware that the computer-generated simulations are not real. This means they are more willing to enter challenging situations and experiment with alternative responses. Importantly, the learning achieved in VR then translates to the real world. VR has been used as an effective treatment for anxiety [4,5] and, more recently, as a treatment for patients with psychosis [6-8]. Automation of VR treatment [5], coupled with the use of consumer hardware, provides an opportunity to increase provision of effective psychological treatments, which are often difficult to access for people with psychosis [9].

Using a socially inclusive design process, the trial team has developed a novel automated VR cognitive treatment targeting anxious avoidance of social situations by people with psychosis: the gameChange therapy (see [10]). The 6-session VR therapy consists of computer simulations of everyday scenarios: a street, a bus, a café, a pub, a doctor's waiting room, and a shop. Each scenario provides an opportunity to test anxious cognitions while limiting the use of defense behaviors, allowing users to gain confidence in their ability to cope. A virtual coach guides the user through the treatment. A member of staff is present to assist the user with the VR equipment and provide encouragement. As the therapy is automated, no formal training in psychological therapy is required to deliver the treatment. A multisite randomized controlled trial testing the gameChange VR therapy is currently underway in five centers in the United Kingdom (Bristol, Manchester, Newcastle, Nottingham, and Oxford) [11]. Critical to evaluating this novel treatment is understanding the participants' experience of engaging in the therapy.

Interpretative phenomenological analysis (IPA) is a qualitative approach that focuses on understanding an individual's lived experience and how they make sense of it [12]. IPA aims to enable the researcher to step into the participant's world and to understand, as far as is possible, how they make sense of an experience [12]. This approach can be extended using peer-research principles, in which the research is steered and conducted by people with relevant lived experiences [13]. A peer research approach can potentially facilitate greater depth and more nuance in data collection and analysis. For example, during the interview, a shared understanding of language and empathy based on similar experiences can enhance rapport, reducing the boundaries between the researcher and the participant [14] and lessening the power balances between them [15]. This can result in the collection of more open, honest, and detailed data [15,16]. During analysis, peers bring different perspectives and insights compared to nonpeer researchers [17-19]. Working collaboratively from multiple perspectives, including a peer perspective, can enhance both the

trustworthiness and the ecological validity of the analysis [17,18].

A multiple perspective design provides a structure to explore different perspectives on an experience while allowing for the homogeneity of the sample, as required for IPA [12,20]. Individual cases will be examined first. Cases of directly related groups will then be examined, such as those who have experienced the same phenomenon (in this case, anxious avoidance and the gameChange intervention). Individuals may have different perspectives on it (eg, those who had a positive experience and those who did not). This design is particularly appropriate when trying to understand "problems in the implementation and translation of effective interventions in specific social or cultural contexts" [21].

We are conducting a qualitative study using a peer research approach to explore experiences of anxious social avoidance and participation in the gameChange VR therapy. A complementary implementation study is being conducted to identify and understand issues affecting how the therapy will be adopted into health care services within the context of the trial.

Objectives

The study has two objectives. The first is to gain an in-depth, first-person perspective on the experience of taking part in the gameChange VR therapy, which is designed to help people build confidence in everyday social situations. This includes understanding (1) the experience of anxious social avoidance in people with psychosis, (2) the experience of the automated VR therapy, and (3) any potential impact of the therapy. The second objective is to explore how peer research approaches can be used to co-create knowledge.

Ethical Review

The gameChange trial, including this qualitative study, received Health Research Authority approval, Health and Care Research Wales approval (IRAS 256895, The gameChange Trial), and ethical approval from the NHS South Central – Oxford B Research Ethics Committee (19/SC/0075). The trial has been registered (ISRCTN17308399) and the protocol published [11].

Methods

To increase the methodological quality and reporting, the presentation of the study will follow the guidance from the 32-item Consolidated Criteria for Reporting Qualitative Research (COREQ) [22].

Patient and Public Involvement

There has been extensive patient and public involvement throughout the gameChange project. This includes the design and conduct of the trial as well as the development of the treatment. For example, more than 50 people with lived experience of psychosis contributed to the design of the gameChange therapy [10]. The Lived Experience Advisory Panel (LEAP), facilitated by the McPin Foundation, advises on the conduct of the project. The LEAP comprises 10 individuals with lived experience of psychosis from across the five study centers.

The LEAP has been involved in the design of this study. To date, the LEAP has contributed to developing the interview schedule, completing pilot interviews, refining the recruitment procedure, and conducting a review of all study documentation (including the information sheet and consent form) for accessibility and clarity. In response to the pilot interviews, the order of the topics was revised. The LEAP will form part of the analysis team and complete sample validation of the data.

Peer Research Methods

This study takes a peer research approach, including employing a researcher with relevant lived experience of psychosis and social anxiety as part of the study team. This individual has not received the gameChange VR therapy but has explored the intervention to become familiar with the participants' experience. They have been involved in developing the research proposal and designing data collection methods, they are interviewing participants, and they will be analyzing data and disseminating findings. Another researcher who has experience of poor mental health but is not a peer in this context will bring their experience of using IPA research methods and a connection to relevant experiences of mental health issues that are generic rather than specific to people with psychosis and social avoidance.

Participants

The participants will be a subsample of approximately 25 people who took part in the gameChange trial as participants. The trial participants are people with psychosis and self-reported difficulties going outside among other people due to anxiety. There are five gameChange trial centers based in NHS mental health trusts across the United Kingdom: Avon and Wiltshire Mental Health Partnership NHS Trust, Greater Manchester Mental Health NHS Foundation Trust, Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust, Nottinghamshire Healthcare NHS Foundation Trust, and Oxford Health NHS Foundation Trust. Participants for this study will be recruited from each of the trial centers. The inclusion criteria are:

- Participating in the gameChange trial and randomized to receive the gameChange VR therapy in addition to usual care.
- Willing to have the interview audio recorded.
- Willing and able to give informed consent to participate in the interview.

The project included people with a psychosis diagnosis attending NHS mental health services who experience anxious avoidance in everyday social situations. The full inclusion and exclusion criteria for participating in the gameChange trial are provided in the published trial protocol [11]. A participant may also not enter the trial if there is another factor that, in the judgement of the investigator, would preclude the participant from providing informed consent or from safely engaging with the trial procedures. Therefore, due to the COVID-19 pandemic, recruitment for people who have any of the conditions that would place them at high or moderate risk (clinically vulnerable) for a severe course of COVID-19 was suspended.

Sampling and Recruitment

Participants will be recruited through the gameChange trial. IPA requires samples to be constructed around a conceptualized shared perspective: in this case, as outlined above, this is operationalized in terms of adults experiencing psychosis and social anxiety, in receipt of NHS mental health care, who have received the gameChange VR therapy.

Multiple perspective designs in IPA allow this homogeneity to be supplemented by some dimensions of further variability, with each conceptualized additional perspective constituting its own subsample. We are recruiting approximately 25 participants, with 3-8 participants from each of the trial centers via liaison with local trial coordinators. This is a relatively large total sample for IPA, but in this study, IPA's commitments to depth of analysis and idiographic detail will be met via the multiple perspective design (allowing the analysis to be developed via 2-4 subsamples) and with the additional support of a template analysis component.

The primary sampling method is to invite consecutive participants as they reach the final phase of the trial. Whenever possible, this will be supplemented by purposive sampling to recruit people with a range of views and experiences of the VR intervention. This will be ascertained through therapy completion rates (low: 0-2 sessions; medium: 3-5 sessions; high: 6-8 sessions).

Sampling will also be sensitive to the demographic characteristics of the participants, aiming for a balance of gender and a range of age and ethnicity. Other dimensions of interest include the profession of the staff member facilitating VR therapy sessions (peer support worker, clinical psychologist, assistant psychologist); location of the treatment delivery (patient home, NHS clinic); and referring clinical service (early intervention; adult mental health; inpatient).

In this study, decisions about the main subsamples for the multiple perspectives design will be made at the midpoint of recruitment. This enables the design to be responsive to the key dimensions of interest emerging from the accounts. These may relate to therapy completion rate or the participants' views of therapy. However, there may be indications that the other contextual/identity features described above are sharpening participants' experiences of the intervention. If these are deemed more important to contrast systematically, the subsamples will be stratified accordingly.

Recruitment Procedure

The trial coordinator at each center will facilitate recruitment. Participants will be invited to participate in the qualitative interview after the first follow-up assessment in the trial (immediately after the therapy window ends). The trial coordinator will provide potential participants with the information sheet in advance. The information sheet states that one of the researchers is a peer. The trial coordinator will introduce the participant to the researchers. The peer researcher will speak to the participant in advance of the interview. This discussion may include a further elaboration on their "peerness," disclosing that they have some experiences in common in relation to the topic being studied, which will be documented in the research log. Written or oral informed consent will be taken at the time of the interview.

Data Collection

Data will be gathered via semistructured interviews. Participants will be given as much choice as possible in how the interview is conducted. The primary method will be to complete the interview remotely, via video or telephone call.

There will be a primary and secondary interviewer. Participants will be told that one of the interviewers has had experiences like those being explored in the gameChange study. The other researcher, who has experience of conducting research interviews for an IPA study, will lead the first interviews. The interviews will be audio recorded. The peer researcher will lead later interviews so that the interviewee will be able to respond directly to the researcher with shared experiences, similar to the approach outlined by Harding et al (2010) [15]. The interviewer with relevant lived experience will decide when, how, and what to disclose about their peerness; this may vary according to how appropriate and comfortable this disclosure feels. Both researchers will document any disclosure of peerness in their field notes and reflect on any changes it made to the interview. These notes will be used in the analysis. At the end of the interview, the participant will be asked whether the presence of a peer researcher made any difference to their decision to participate and whether they thought it had an impact on their experience of the interview.

Peer researchers, qualitative researchers, implementation researchers, clinical psychologists, and members of the gameChange LEAP contributed to the development of the interview schedule. The development process included a review of the literature on anxious avoidance in people with psychosis, consideration of the key principles and novel features of the gameChange treatment, the complementary implementation study, and routes to include peer research methods within the interview. For example, in preparation for the interviews, the two researchers who will be collecting the data interviewed each other about their relevant lived experience. This provided potentially valuable insights into how to approach topics and ensure the phrasing was understandable and engaging. The interview schedule was further refined following pilot interviews with members of the LEAP.

The interview schedule was designed in line with IPA and phenomenological approaches [23,24], employing both open-ended descriptive and narrative questions to provide context (eg, "Tell us about what was going on in your life before you started the gameChange VR therapy?") and descriptive/structural questions (eg, "Can you walk us through a typical gameChange VR therapy session?"). Open-ended questions are followed by individually tailored prompts to elicit further information and clarification.

Analysis

IPA and Template Analysis

A total of 6 transcripts will be coded using interpretative phenomenological analysis (IPA) [12,25], and the remaining transcripts will be analyzed using template analysis [20]. A

multiple perspectives design will be employed and a peer research approach will be taken, which includes collaborating with the LEAP throughout the analysis.

IPA aims to enable the researcher to step into the participant's "lifeworld" [12] to understand, as far as is possible, how they make sense of an experience and contextualize it against the background of their lives. IPA is idiographic in that it focuses in-depth on the individual account before looking for convergence and divergence across the sample. Template analysis is a flexible approach that can be used in concert with IPA to enable larger samples to be analyzed [26]. The multiple perspectives design provides a structure for exploring both the individual case and considering cases of directly related groups [21].

IPA complements a peer research approach because it acknowledges the role of the researcher in the interpretation of the data and resulting themes. The researcher will try to make sense of the participant trying to make sense of what has happened to them. Reflexivity is welcomed. Having multiple members of the research team conduct the analysis, including those with aspects in common with the participants, will increase the depth and sensitivity of the analysis [17].

Analytic Method

A total of 6 transcripts will be chosen for IPA by the interviewers and the wider analysis team, based on the richness of the data and the chosen perspective (eg, participants with a positive view of the experience). The IPA will adopt analytic strategies described by Larkin and Smith (2011) [25] and Smith, Flowers, and Larkin (2021) [12]. The interviews will be transcribed verbatim. Analysis will be primarily conducted by the two interviewers, with additional input from DR, ML, SL, and FW as well as from the wider research group and the LEAP. Taking a case-by-case approach, transcripts and reflective interview notes will be read and reread. Line-by-line annotation on the participant's claims, concerns, and understandings will be made by the two researchers. These notes require close reading and interpretation on the part of the researcher, dovetailing with the peer research approach. Annotation will identify the things that matter to each participant and the meanings associated with those things. These meanings will then be clustered and interpreted for each case. Once this process has been completed for the first interview, it will be repeated for each subsequent participant (6 cases overall). This will be used to develop themes that encompass the phenomenological experiences and understandings across the accounts of the first 6 participants. The two researchers performing the analysis will be in contact but will conduct independent analyses of the 6 transcripts. This will result in two sets of themes, one from a peer perspective.

Multiple coding can reveal new insights and explanations, especially if the researchers have different backgrounds and, therefore, different standpoints, resulting in a richer interpretation of the data [18]. The two sets of themes will be discussed and revised accordingly following review by the wider research team, including the LEAP, implementation researchers, clinical psychologists, and a qualitative research expert. The LEAP will contribute to the analysis by reviewing the preliminary themes and supporting quotes, commenting on what strikes them as interesting and the extent to which the researchers' interpretations of the data resonate with their own [27]. Notes will be kept about any decisions made due to these meetings.

After these discussions, a provisional "template" will be agreed upon. This will be used to initiate the template analysis on the remaining data. The template evolves iteratively as more of the data are coded. Honoring the multiple perspective design, we will introduce each of the remaining groups of transcripts (based on treatment completion/uptake) one at a time, focusing on each in turn. After each group has been analyzed, we will review the template to see whether it needs to be updated as a result. We will use the steps outlined by King et al (2004) [28], namely moving systematically through the transcripts to identify data that are relevant to the research aims, assigning one or more codes from the template, and reviewing and updating the template at appropriate intervals. Once all the data have been coded and the template finalized, all transcripts will be reviewed and recoded as needed. The LEAP will again be consulted. NVivo software (QSR International) will be used to organize the data.

The result will be a set of themes (the finalized template) that represents all interviews, 6 of which will also be in case study format from the IPA. The "lamination," or layering, made feasible by this dual approach of IPA and template analysis within a multiple perspectives design will give the study both depth and breadth. All transcripts will be deleted after the analysis is complete.

Credibility

The four criteria for "trustworthiness" in qualitative research (credibility, transferability, dependability, and confirmability) will be monitored and addressed [29]. To increase credibility, sample validation will be conducted with members of the gameChange LEAP. The contextual constructivist position that we adopt, and the IPA methodology, assume that the data are specific to the context and time that they were collected [12,30]. However, by providing a description of this context—including information about the location (the five trial centers), participant demographic information, illustrative extracts, and situation of the findings in relation to existing literature—the reader should be equipped to evaluate how transferable the findings are to other groups and locations. Reflexive logs will be maintained throughout the research process to explore how each researcher's background, presentation, interests, existing assumptions, and peerness have impacted the study. The logs will be used to capture initial thoughts after each interview and during the analysis process, as well as to document and justify methodological decisions. The reflexive logs, transcripts, interview schedule development, and minutes of the supervisory research team meetings will provide an audit trail of the analysis.

Reflexivity

All researchers conducting the interviews or analysis will consider how their own backgrounds may impact data collection and analysis. This will require the researchers to reflect on the different perspectives that they are bringing to the study design,

setup, data collection, and analysis. Details of the research team and reflexivity will be reported in the full manuscript in line with COREQ guidelines [22].

The research team includes a peer researcher, a nonpeer researcher, clinical psychologists who have been involved in the design and use of VR therapy, implementation researchers who are conducting a complementary study on the use of the gameChange VR therapy in mental health services, and a qualitative researcher who has pioneered the IPA approach. Therefore, existing knowledge, experiences, and hopes regarding VR therapy may impact the conduct of the interviews and analysis. We have explicitly set out to use the peer knowledge and examine peer research methods in this study. Therefore, the two interviewers will each keep a reflexive log to document the use of peerness during data collection and analysis.

Assessing Peer Research Methods

The secondary methodological objective of this study is to learn about peer research methods and co-creation of knowledge. We will investigate the impact of peerness from overlapping, related, and nonpeer perspectives. This includes (1) how peerness is negotiated and disclosed throughout interactions with participants, (2) the effect of peerness on the interview and data collection process, and (3) the impact on analysis. This will be achieved by drawing on the researcher logs and interview field notes, evaluating participant feedback at the end of the interview (when asked about the experience of being interviewed by a peer), and discussing sections of the transcripts that document disclosure of peerness with the LEAP. To assess the impact of peer methods on the analysis, we will compare the two sets of themes resulting from the independent analysis by the two interviewers to explore key differences and similarities in the insights and interpretations. However, to identify differences based on research expertise or identity, a much larger group of peer and nonpeer coders would be required [17], which is not feasible within this study.

Results

Data collection will be conducted from April to September 2021, with analysis performed from June to October 2021. As of September 28, 2021, data collection with 20 participants had been conducted, and coding is underway. This study is expected to conclude in 2022.

Discussion

This protocol describes the plan for a multisite qualitative study using peer methods to explore experiences of anxious social avoidance in the context of psychosis and its treatment using an automated VR cognitive therapy program: the gameChange treatment. The gameChange VR cognitive therapy is designed to help people build confidence in everyday social situations. The qualitative study is being conducted in the context of VR therapy being tested in a multisite randomized controlled trial [11]. This study will provide insight into the individual experience of receiving novel automated VR therapy. Understanding the participant experience is likely to prove to be key to facilitating uptake in future implementation in mental health services. This understanding will be achieved using peer research methods, ensuring people with lived experience of psychosis are at the center of the research.

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Conflicts of Interest

DF is a founder and nonexecutive board director of Oxford VR, a University of Oxford spin-out company, which programmed and commercializes the gameChange treatment. DF holds equity in Oxford VR. SL does consultancy work for Oxford VR. The McPin Foundation will receive an IP payment from Oxford VR due to their role in the therapy development for the gameChange study.

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
IPA: interpretative phenomenological analysis
LEAP: Lived Experience Advisory Panel
NHS: National Health Service
NIHR: National Institute for Health Research
PPI: patient and public involvement
VR: virtual reality

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Protocol

Assessment of an Innovative Mobile Dentistry eHygiene Model Amid the COVID-19 Pandemic in the National Dental Practice–Based Research Network: Protocol for Design, Implementation, and Usability Testing

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Abstract

Background: Amid COVID-19, and other possible future infectious disease pandemics, dentistry needs to consider modified dental examination regimens that render quality care, are cost effective, and ensure the safety of patients and dental health care personnel (DHCP). Traditional dental examinations, which number more than 300 million per year in the United States, rely on person-to-person tactile examinations, pose challenges to infection control, and consume large quantities of advanced-level personal protective equipment (PPE). Therefore, our long-term goal is to develop an innovative mobile dentistry (mDent) model that takes these issues into account. This model supplements the traditional dental practice with virtual visits, supported by mobile devices such as mobile telephones, tablets, and wireless infrastructure. The mDent model leverages the advantages of digital mobile health (mHealth) tools such as intraoral cameras to deliver virtual oral examinations, treatment planning, and interactive oral health management, on a broad population basis. Conversion of the traditional dental examinations to mDent virtual examinations builds upon (1) the reliability of teledentistry, which uses intraoral photos and live videos to make diagnostic decisions, and (2) rapid advancement in mHealth tool utilization.

Objective: In this pilot project, we designed a 2-stage implementation study to assess 2 critical components of the mDent model: virtual hygiene examination (eHygiene) and patient self-taken intraoral photos (SELFIE). Our specific aims are to (1) assess the acceptance and barriers of mDent eHygiene among patients and DHCP, (2) assess the economic impact of mDent eHygiene, and (3) assess the patient's capability to generate intraoral photos using mHealth tools (exploratory aim, SELFIE).

Methods: This study will access the rich resources of the National Dental Practice-Based Research Network to recruit 12 dentists, 12 hygienists, and 144 patients from 12 practices. For aims 1 and 2, we will use role-specific questionnaires to collect quantitative data on eHygiene acceptance and economic impact. The questionnaire components include participant characteristics, the System Usability Scale, a dentist-patient communication scale, practice operation cost, and patient opportunity cost. We will further conduct a series of iterative qualitative research activities using individual interviews to further elicit feedback and suggestion for changes to the mDent eHygiene model. For aim 3, we will use mixed methods (quantitative and qualitative) to assess the patient's capability of taking intraoral photos, by analyzing obtained photos and recorded videos.

Results: The study is supported by the US National Institute of Dental and Craniofacial Research. This study received "single" institutional review board approval in August 2021. Data collection and analysis are expected to conclude by December 2021 and March 2022, respectively.

Conclusions: The study results will inform the logistics of conducting virtual dental examinations and empowering patients with mHealth tools, providing better safety and preserving PPE amid the COVID-19 and possible future pandemics.

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KEYWORDS

teledentistry; mDentistry; oral diseases; virtual visit; intraoral camera; pandemic response; COVID-19; mHealth

Introduction

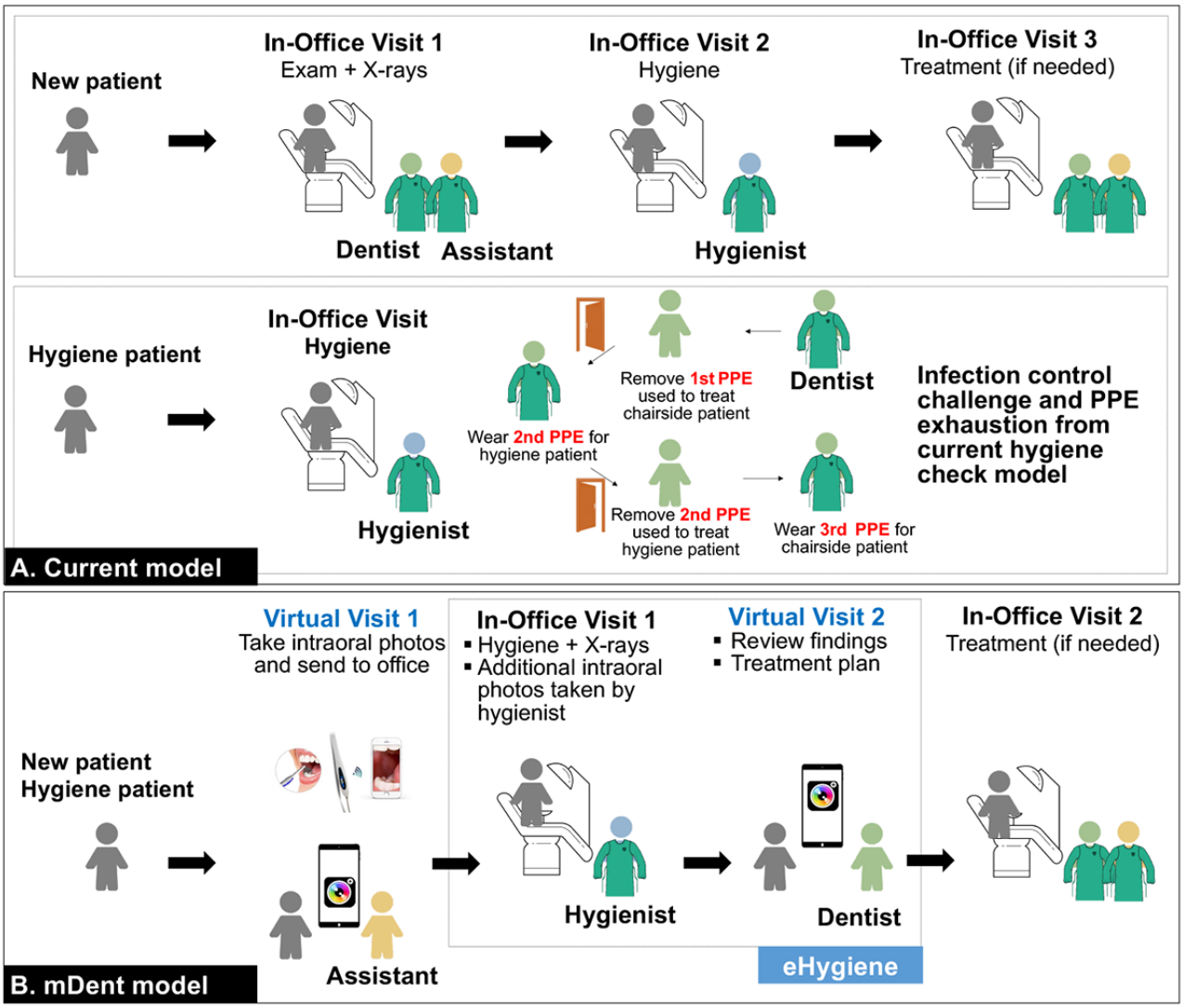
Urgent Need to Transform the Dental Visit Format During Infectious Disease Outbreaks

Amid the COVID-19 pandemic, dental health care personnel (DHCP) are at great risk of contracting the SARS-CoV-2 virus due to their close physical proximity to their patients, as well as the enhanced potential for transmission of airborne viruses in the dental setting [1]. When delivering dental services, DHCP consume increased amounts and enhanced levels of personal protective equipment (PPE), equivalent to the ones used by other health care providers who provide care to COVID-19–positive patients. This PPE includes N95 respirators, goggles, gowns, head covers, and face shields. Although dentistry has practiced for years utilizing person-to-person visual-tactile examinations, now, more than ever, utilizing a wide variety of new technologies and approaches to deliver virtual dental services would have significant utility.

Aggressively converting traditional dental examinations (eg, comprehensive, limited, and hygiene recall examinations) to virtual examinations could significantly reduce the exposure risk for patients and DHCP and preserve a large volume of PPE essential to the medical and dental communities. According to the American Dental Association, as of 2019, 200,419 dentists were practicing dentistry in the United States, with 158,331 (79%) general dentists (GD) providing a range of examination visits on a daily basis [2]. GDs in the United States are conducting 564 million patient visits per year (an average of 3566 patient visits per GD) [3]. Importantly, 316 million of these 564 million patient visits (56%) are examination visits. These visits comprise 67 million (21%) new patient examinations, 40 million (13%) limited examinations, and 209 million (66%) hygiene recall examinations, which are often not linked to definite treatment delivery at the same visit. If these 316 million examinations were all (or partially) converted to virtual visits, serving as remote triage of patients' needs, 316 million person-to-person contacts would be avoided, preserving at least 1 billion pieces of PPE per year.

In the current dental examination model (Figure 1), patients often need to have one examination visit and one hygiene visit before they get to a definite treatment visit. A dentist hygiene check visit usually includes x-rays taken by the dental hygienist and an examination completed by the dentist [4]. In a regular dental office, the dentists usually conduct hygiene examinations in between treating their chairside patients [4]. In the current COVID-19 environment and for the foreseeable future, the dentist needs to change PPE between seeing his or her chairside patient and the hygiene patient and then change to another PPE when completing the hygiene check and returning to the original chairside patient. A single hygiene check examination consumes 2 sets of PPE for the dentist alone and increases the challenge of infection control due to frequent switching of PPE and the dentist running between dental operatories. Moreover, with added time from changing PPE, extended waiting can add more frustration to that already reported by patients and dental hygienists while waiting for dentists during traditional hygiene examinations [4]. Dentistry needs changes to the dental examination regimens, especially hygiene examinations, to render quality care and ensure the safety of patients and the DHCP amid the COVID-19 outbreak.

Figure 1. Current and proposed mobile dentistry (mDent) model for dental examinations. PPE: personal protective equipment.



Rationale for Developing the mDent eHygiene Model in a Digital Era

Our long-term goal is to develop an innovative mobile dentistry [5] (mDent) model in this digital era (illustrated in Figure 1). The mDent model refers to the practice of dentistry supported by mobile devices such as mobile telephones, tablets, personal digital assistants, and a wireless infrastructure. The mDent model combines virtual dental visits with the use of digital mobile health (mHealth) tools, such as intraoral cameras, to complete oral health screening, treatment planning, virtual hygiene examinations, and interactive oral health education, on a broad population basis. In the mDent model, before patients arrive at the dental office, they would have a virtual visit with dental office personnel to take a series of intraoral photos at home. Capable patients could do this independently by watching a photo-taking tutorial video, minimizing DHCP instruction time during a virtual visit. With the intraoral photos, the DHCP would have a preliminary idea of the patient's oral health. The second visit would be an in-office hygiene visit conducted by the dental hygienist to complete intraoral x-ray records, a soft and hard tissue examination, and additional intraoral photos, if needed. Patients will then have a virtual dental visit, scheduled at a convenient time with the dentist, to review the findings and treatment plans before they proceed with an in-office visit to confirm the examinations and receive a definite dental treatment plan and dental treatment, as appropriate.

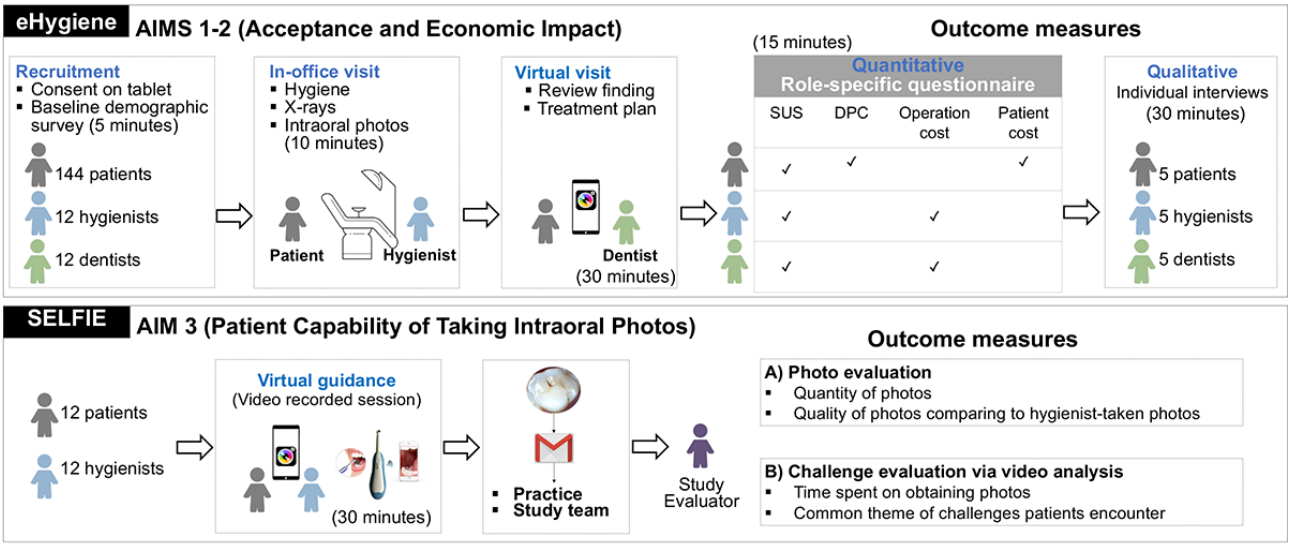
This mDent model will fully engage relevant stakeholders (patients, dental hygienists, and dentists) to conduct interactive oral health practices. The mDent model will also utilize a patient-driven mobile device to increase the accessibility of dental care. Moreover, in the era of COVID-19 risk, this remote virtual dental service model will lead to a well-planned dental service, better infection control, and reduced PPE consumption. As this eHygiene implementation study is a hypothesis-generating pilot study, our immediate objective is to assess the following 3 aims in the National Dental Practice-Based Research Network [6]: (1) Aim 1 is to assess the acceptance and barriers of mDent eHygiene among patients and DHCP, (2) aim 2 is to assess the economic impact of mDent eHygiene, (3) and aim 3 is to assess patients' capability for generating intraoral photos using mHealth tools (SELFIE).

Methods

Overall Study Design

This study will use a 2-stage implementation study to assess the acceptance of 2 components (eHygiene and SELFIE) of the mDent eHygiene model among patients and DHCP (dentists and dental hygienists). The components are illustrated in Figure 2.

Figure 2. Specific aims, study design, and outcome measures. DPC: dentist-patient communiation; SUS: System Usability Scale.



This mDent eHygiene study will use mixed methods (quantitative and qualitative) to collect outcome measures and conduct data analysis. For details, see Table 1 and the following subsections.

Table 1. Mobile dentistry (mDent) model eHygiene objectives and outcome measures.

Aims	Outcome measurements	Brief description and justification of the outcome measures
Aim 1: assess the acceptance of and barriers to mDent eHygiene among patients and DHCP[a]	System Usability Scale (SUS); dentist-patient communication (DPC); theme of acceptance and barriers analyzed from individual qualitative interviews with the DHCP	The SUS instrument will be used to assess the acceptance of the mDent eHygiene approach. The SUS instrument [7-9] is widely adopted in business and technology industries and mHealth[b] fields to measure and quantify the perception of product and service usability. The DPC component will be used to assesses how well the patients understand the planned treatment and the quality of the communication between the patients and dentists using eHygiene. We will use a modified questionnaire from a validated DPC questionnaire [10]. Qualitative analysis will be conducted for data from 15 individuals (5 patients, 5 dentists, 5 dental hygienists) via 30-minute virtual individual interviews. The questions during the interview will address the feedback, perceived challenges, and suggestions for improvement for the mDent eHygiene model.
Aim 2: assess the economic impact of mDent eHygiene	PPE[c] consumption and estimated cost and eHygiene chair time per patient; eHygiene virtual visit time per patient; DHCP (dentist and dental hygienist) personnel cost related to eHygiene	Studies from other groups have shown improved cost-effectiveness using virtual dental visits [11,12]. Now, facing the PPE shortage amid the COVID-19 outbreak, the economic benefits of mDent eHygiene are promising. The magnitude, however, must be carefully evaluated, which will be assessed using the outcome measured listed in this objective via role-specific baseline and post-eHygiene questionnaires.
Aim 3: assess patients' capability for generating intraoral photos using mHealth tools (SELFIE)	Quantity and quality of intraoral photos taken by patients, assessed by 1 dentist in the study team who will be trained for photo assessment; themes of challenges encountered by patients while taking intraoral photos themselves, by analyzing the video recordings from the SELFIE session	This objective will provide preliminary data on patient engagement with using mHealth tools, which is essential to empowering patients in the complete mDent model.

[a]DHCP: dental health care personnel.

[b]mHealth: mobile health.

[c]PPE: personal protective equipment.

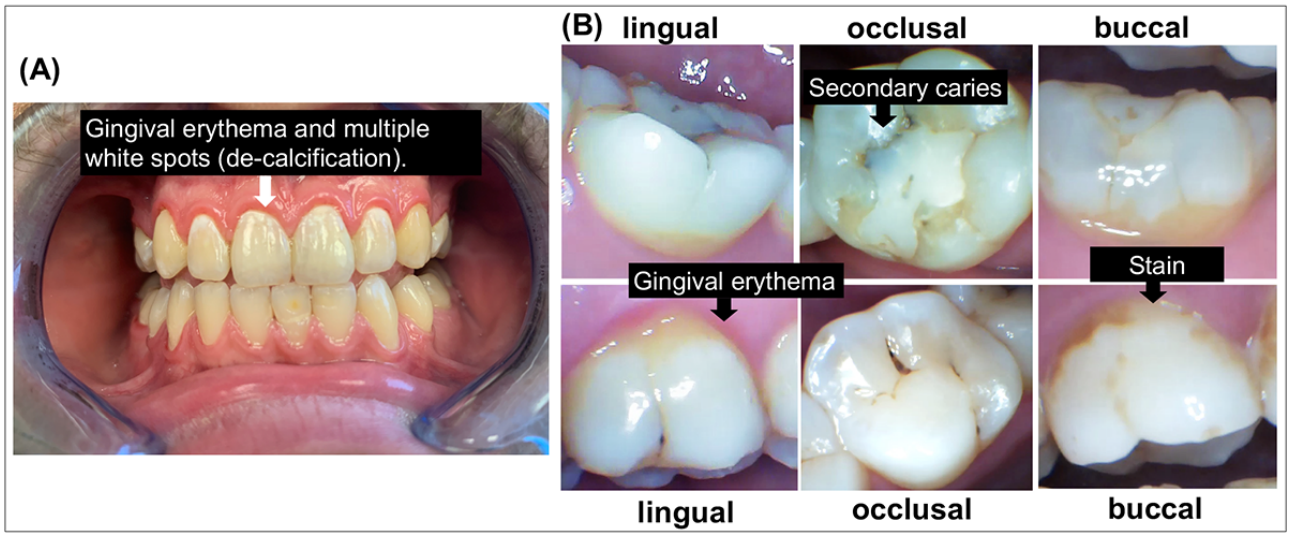
Participants and Recruitment

The mDent eHygiene study will be conducted in the Northeastern node of the National Dental Practice-Based Research Network in the United States. This mDent eHygiene study will enroll 144 patients and 24 DHCPs from 12 practices. Each practice will enroll 12 patients, 1 dentist, and 1 dental hygienist. All 144 patients and 24 DHCPs will conduct the eHygiene session (1st stage) of the study. Among enrolled patients and DHCPs, 5 patients, 5 dentists, and 5 dental hygienists will be invited for a 30-minute recorded telephone interview for a qualitative session of the eHygiene study. In addition, 12 patients will be invited to conduct a SELFIE session to evaluate their capability for taking intraoral photos by themselves, with guidance from the dental hygienist.

Intraoral Photo Taken by a Dental Hygienist in an eHygiene Session

The dental hygienist will complete a routine hygiene visit, update x-rays, and perform a hard and soft tissue examination as part of routine clinical care. Intraoral photos of patients will be taken for research purposes following a recommended template (See Multimedia Appendix 1). Intraoral photos will be stored in Mouthwatch Teledent—a cloud-based platform for conducting Teledent visits. A series of intraoral photos will be taken by a tablet and an intraoral camera connected to a tablet. Examples of intraoral photos are shown in Figure 3.

Figure 3. Patient self-taken intraoral photos: (A) front view taken on an iPhone X, on which gingival erythema and multiple white spots (de-calcification) are seen; (B) posterior photos taken with a Mouthwatch intraoral camera, where the upper panel includes photos of the lower left first molar and lower panel photos of the upper right first molar.



Patient-Dentist Virtual Visit in the eHygiene Session

The dentist will then conduct a virtual visit with the patient lasting approximately 30 minutes at a later and suitable time within 14 days of the eHygiene intraoral photo visit, to review eHygiene findings and treatment plans.

SELFIE Session

The self-taking of intraoral photos (SELFIE session) will be piloted by 12 (1 from each practice) of the 144 study patients who complete the eHygiene session. The intraoral camera and instructional video will be given to the patient when the patient leaves the hygiene visit. During a virtual visit with the dental hygienist, the patient will use an intraoral camera while being supervised by the dental hygienist to take a series of intraoral photos of the front and posterior teeth. This virtual visit session will be recorded.

Patients will be encouraged to think-aloud [13] about their feelings and difficulties encountered while taking photos. The think-aloud process asks users to verbalize their thoughts as they complete various tasks, allowing investigators to gain insight on participants' thought processes in relation to the technology products.

Study Questionnaires

Each participating patient, dentist, and dental hygienist will complete baseline and post-eHygiene role-specific questionnaires (see Multimedia Appendix 2 for the dentist questionnaire, Multimedia Appendix 3 for the hygienist questionnaire, and Multimedia Appendix 4 for the patient questionnaire) as per the study schedule. The questionnaires include the System Usability Scale (SUS), dentist-patient communication (DPC) scale, office operation, and other items detailed in Table 1.

Qualitative Interviews

After receiving the SUS scores from all patients and DHCPs, the study team will randomly select 15 individuals (5 patients, 5 dentists, 5 hygienists) for virtual individual interviews lasting approximately 30 minutes. These 15 individuals will include those who rated above and below the average SUS score. The questions asked during the interview will address feedback and recommendations, perceived challenges, and suggestions for improvement of the mDent eHygiene model. The interviews will be standardized using an interview guide (see Multimedia Appendix 5), and interviews will be audio-recorded.

Statistical Analysis

Sample Size Considerations

The sample size calculation for the primary outcome (eHygiene—SUS) was based on the primary outcome of the SUS score from patients. Various studies [7,14,15] have used the SUS scale to assess the usability of a medical service or mHealth tool and reported mean SUS scores of 47.5-81.2 (SD 9.9-21.1). Since the patients in the eHygiene study are clustered by practice, we used a cluster randomized design calculation for the sample size calculation. Assuming the difference in the SUS score between the patient-evaluated eHygiene model and other published mHealth tools has a mean of 8 and an SD of 10, a sample size of 72 patients from 12 practices (6 per practice) will achieve 90% power, at an alpha of .05. Considering the potential dropout rate, a sample size of 144 patients will satisfy the statistical power of the primary outcome.

Dentists and dental hygienists will complete the SUS for each patient when the dentist and hygienist complete an eHygiene visit, which means each dentist and hygienist will evaluate the eHygiene model 12 times. Assuming a mean difference of 30 (SD 20) between the first and last patients evaluated by the dentists and hygienists, using a paired *t* test, a sample of 7 dentists or hygienists will achieve 90% power, at an alpha of .05. Considering potential dropouts, recruiting 12 dentists and 12 dental hygienists will achieve satisfactory statistical power for this aim.

Using a cluster randomized design to calculate the sample size for the primary outcome of DPC and assuming a mean difference in the patient-evaluated DPC score between the current hygiene model and the eHygiene model of 8 (SD 10), a sample size of 48 patients from 12 practices (4 per practice) will achieve 85% power, at an alpha of .05. A sample size of 144 patients will satisfy the statistical power of the DPC outcome, while considering potential dropouts.

For the sample size calculation of the tertiary outcome (SELFIE), we expect to reach data saturation [16] (no new themes are identified) after conducting 12 individual tests. The sample size was determined based on previously published studies, where between 6 and 11 usability tests were conducted to assess technology products, for instance, smartphone app usability [17,18].

Analyses for Aim 1: eHygiene

We will calculate SUS scores for the eHygiene model (post-eHygiene SUS) as rated by patients, dentists, and dental hygienists. The SUS score from the patients and DHCPs between practices will be compared. A linear mixed effects model will be used to examine factors that influence the SUS score as perceived by patients, including patient factors (demographic, socioeconomic, education, profession, and experience with using a digital device and mHealth tools) and DHCP factors (demographic and dental practice experience), while considering the clustering effects within practices and providers. The eHygiene SUS score as rated by dentists and dental hygienists from treating the first patient through the last study patient will be compared to assess whether the DHCP-determined SUS score is associated with a learning curve.

We will calculate the DPC score as rated by patients, which assesses how well the patients understand the planned treatment and the quality of the communication between the patients and dentists who participate in eHygiene. We will use a linear mixed effects model to examine factors that influence the DPC score perceived by patients, including patient factors (demographic, socioeconomic, education, profession, and experience with using a digital device and mHealth tools), DHCP factors (demographic and dental practicing experience), and time spent on the eHygiene visit, while controlling for the clustering effects within practices and providers. We will run separate models for patients and DHCP.

Regarding qualitative data, the interviews will be standardized using interview guides, audio-recorded, transcribed, coded, and analyzed for thematic content. The audio recordings will be transcribed by the Temi (San Francisco, CA) transcription service and further verified by 2 trained research personnel. Transcribed data will be analyzed using MAXQDA software (VERBI GmbH, Berlin, Germany). The data will be coded by 2 trained coders with predetermined open codes using a codebook with a description of the coding tree. Thematic content will be further analyzed using categorizing and contextualizing strategies to understand the factors associated with acceptance of and barriers to eHygiene among patients and DHCPs.

Analyses for Aim 2: Economic Impact

We will conduct analysis for the following parameters: (1) PPE consumption and estimated cost and comparison between eHygiene and traditional hygiene examination models for each practice; (2) eHygiene chair time per study patient, learning curve–related fluctuations in chair time per practice, and comparisons between practices; (3) eHygiene virtual visit time and comparison between practices; and (4) DHCP (dentist and dental hygienist) personnel cost related to eHygiene in-office and virtual visits, compared with traditional hygiene examination visits.

Analysis for Aim 3: SELFIE Intraoral Photos

Parameters to be evaluated include time spent on photo taking, number of photos, and readable photos by a dentist evaluator using a photo assessment from (Multimedia Appendix 6). Factors including patient demographic, education, and experience with using a digital device and mHealth tools that potentially relate to patient capability will be further assessed.

The “think-aloud” videos recorded during the SELFIE sessions will be reviewed by a trained study evaluator to analyze common themes of challenges patients encounter, using a SELFIE assessment form (Multimedia Appendix 7). The key tasks are connecting cameras with a tablet, locating the photo-taking module in the TeleDent software, using a cheek retractor, taking front-view and posterior teeth photos, and ensuring photos are stored in the TeleDent software. User performance for these key tasks will be ranked as critical (requiring assistance to proceed), severe (major delay and/or frustration), or cosmetic (minor) and annotated to the specific task. Based on rankings,

the team will suggest changes to the instructional video and clinic procedures for future implementation.

Results

The study has been peer-reviewed and funded by the US National Institute of Dental and Craniofacial Research. This study received single institutional review board approval from the University of Alabama at Birmingham (#300006506) and local context review from the University of Rochester (#6077). The eHygiene study is expected to launch in August 2021. Data collection and analysis are expected to conclude by December 2021 and March 2022, respectively.

Discussion

Study Innovation

This study is innovative in several ways. First, conducting virtual dental examinations (the mDent model) using intraoral photos and x-rays is novel and potentially transformative to dental practice. Using smartphones and mobile devices to take photos of the mouth and teeth and conduct oral disease screening has been recently reported [19-21]; however, the feasibility of engaging dental hygienists and patients to obtain intraoral images using an intraoral camera has not been assessed. Second, transforming the traditional one-on-one tactile dentist examination to an eHygiene visit requires a team effort from several stakeholders: the patient, dental hygienist, and dentist. This level of teamwork in dental offices is innovative. The team effort could lead to better DHCP-patient communication and a better understanding and compliance with this approach to dental treatment. Third, integrating the mHealth concept into dentistry to achieve population-wide oral health screening and monitoring is extremely innovative and offers a vehicle to promote patient-engaged oral health education and patient-driven early detection of oral disease. Fourth, the eHygiene model is a novel way of preserving PPE during the COVID-19 and other respiratory-transmissible disease outbreaks.

Impact on Clinical Practice

Successful completion of this eHygiene pilot study will provide data on the acceptance and economic impact of virtual dental examinations during eHygiene visits, which will be a test vehicle for the future mDent model. The results will inform potential immediate modification of the dental service system to provide better safety and preserve PPE amid COVID-19 and other infectious disease outbreaks and beyond.

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Authors' Contributions

JX, CM, DTK, TTW, and KF contributed to the conception; design; data acquisition, analysis, and interpretation; and drafting and critically revising the manuscript. PR, KF, TRL, LAMC, EI, MS, and the National Dental Practice-Based Research Network Collaborative Group contributed to data acquisition, data analysis, and critically revision of the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work. An internet site devoted to details about the National Dental Practice-Based Research Network is located at [22].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intraoral photo taking template.
[DOCX File , 3823 KB - resprot_v10i10e32345_app1.docx]

Multimedia Appendix 2
Dentist role-specific questionnaire.
[DOCX File , 38 KB - resprot_v10i10e32345_app2.docx]

Multimedia Appendix 3
Hygienist role-specific questionnaire.
[DOCX File , 37 KB - resprot_v10i10e32345_app3.docx]

Multimedia Appendix 4
Patient role-specific questionnaire.
[DOCX File , 39 KB - resprot_v10i10e32345_app4.docx]

Multimedia Appendix 5
Qualitative interview guide.
[DOCX File , 37 KB - resprot_v10i10e32345_app5.docx]

Multimedia Appendix 6
SELFIE session intraoral images assessment form.
[DOCX File , 28 KB - resprot_v10i10e32345_app6.docx]

Multimedia Appendix 7
SELFIE session video assessment form.
[DOCX File , 30 KB - resprot_v10i10e32345_app7.docx]

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Abbreviations

DHCP: dental health care personnel
DPC: dentist-patient communication
GD: general dentist
mDent: mobile dentistry
mHealth: mobile health
NIDCR: National Institute of Dental and Craniofacial Research
PPE: personal protective equipment
SUS: System Usability Scale

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Protocol

Understanding the Associations of Prenatal Androgen Exposure on Sleep Physiology, Circadian Proteins, Anthropometric Parameters, Hormonal Factors, Quality of Life, and Sex Among Healthy Young Adults: Protocol for an International, Multicenter Study

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Abstract

Background: The ratio of the second finger length to the fourth finger length (2D:4D ratio) is considered to be negatively correlated with prenatal androgen exposure (PAE) and positively correlated with prenatal estrogen. Coincidentally, various brain regions are sensitive to PAE, and their functions in adults may be influenced by the prenatal actions of sex hormones.

Objective: This study aims to assess the relationship between PAE (indicated by the 2D:4D ratio) and various physiological (sex hormone levels and sleep-wake parameters), psychological (mental health), and sexual parameters in healthy young adults.

Methods: This study consists of two phases. In phase 1, we will conduct a survey-based study and anthropometric assessments (including 2D:4D ratio and BMI) in healthy young adults. Using validated questionnaires, we will collect self-reported data on sleep quality, sexual function, sleep chronotype, anxiety, and depressive symptoms. In phase 2, a subsample of phase 1 will undergo polysomnography and physiological and genetic assessments. Sleep architecture data will be obtained using portable polysomnography. The levels of testosterone, estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, prolactin, melatonin, and circadian regulatory proteins (circadian locomotor output cycles kaput [CLOCK], timeless [TIM], and period [PER]) and the expression levels of some miRNAs will be measured using blood samples. The rest and activity cycle will be monitored using actigraphy for a 7-day period.

Results: In Poland, 720 participants were recruited for phase 1. Among these, 140 completed anthropometric measurements. In addition, 25 participants joined and completed phase 2 data collection. Recruitment from other sites will follow.

Conclusions: Findings from our study may help to better understand the plausible role of PAE in sleep physiology, mental health, and sexual quality of life in young adults.

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KEYWORDS

digit ratio; sleep; sex hormones; testosterone; estrogen; circadian proteins; circadian rhythm; chronotype; miRNA

Introduction

The Activational and Organizational Hypothesis

Sexual differentiation of the brain largely occurs before birth, and this process primarily occurs during short periods when the brain is most sensitive to hormones. In humans, this happens in midpregnancy and the first 3 months after birth [1]. The *Organizational and Activational Hypothesis* suggests that the action of androgens during a sensitive period would have a permanent impact on the brain (*organizational* effect) and would eventually determine how one responds to gonadal hormones during and after puberty (*activational* effect) [2]. One well-documented evidence for this hypothesis is the sex difference in rodent sex behavior. Phoenix et al [3], in their seminal paper, reported that female rat pups that were exposed to testosterone during pregnancy displayed male sexual behavior in adulthood. Later, Feder and Whalen [4] found that male pups that were castrated shortly after birth (but still within the sensitive period) showed feminine sexual behavior as adults.

The exposure to androgens (eg, testosterone) before birth also influences the digit ratio (DR) or the ratio of finger lengths of the second and fourth digits (2D:4D) [5]. Studies on DRs were sparked by the study by Manning et al [6], which reported that the male DR is smaller than the female DR on average. The sex difference in DR appears in the first trimester and is thought to be influenced by androgens [7]. It remains relatively fixed during rapid growth in childhood and puberty. Therefore, postnatal DRs can be used as markers of prenatal androgen exposure (PAE).

Given the early event of sexual differentiation in the brain, various studies have shown that PAE, using DR as a marker, is associated with psychological conditions, including anxiety [8] and depression [9,10]. In this study, we plan to better understand the association of PAE with sleep and sexual functions as well as sexual attraction.

Sleep and PAE

PAE may also influence sleep function in adults, but the evidence is minimal. Studies in rodents [11,12] indicated that, when treated with estradiol and progesterone in adulthood, male rats castrated neonatally (still within the sensitive period) have similar sleep outcomes (ie, nonrapid eye movement [nREM] sleep amount) to female rats, as compared with male rats orchiectomized as adults. This suggests that PAE may influence adult sleep function in response to sex steroid hormones. In addition, circumstantial evidence shows that lower PAE may be linked to more sleep difficulties, as insomnia is more common in females than in males [13]. Furthermore, if our DR hypothesis is supported by findings in this study (ie, androphilic attraction is associated with less PAE), our finding may help explain, from a biological perspective, why sleep deprivation is more common among men with androphilic attraction [14-16]. Undoubtedly, we also need to recognize that sleep problems in sexual minority populations can also be attributed to other factors such as discrimination and depression.

Verster et al [17] found no association between DR and sleep in females, but the right DR was positively correlated with total sleep time in males. However, the study had a number of limitations; for example, it did not include quantitative sleep measurements, and the analyses did not appear to take into account various factors such as age, BMI, and sexual orientation. In this study, we aim to conduct a rigorous study to determine whether PAE, indicated by the DR, is associated with subjective and objective sleep parameters.

Sleep

Sleep is a state of unconsciousness, mandatory for everyone, that can be influenced by external auditory, sensory, or other stimuli. The role of sleep in general health has not been fully examined. Researchers connect sleep deprivation, especially chronic sleep loss, with numerous health problems such as obesity [18], diabetes [18,19], mental diseases [18,20], hypertension [21], cardiovascular events [22], and even common cold [23]. These relationships also point out some important roles of sleep in health. Sleep helps to maintain an efficient immune system [18,23,24], consolidate memory, and clean metabolites from the brain that aggregate during daytime [18]. Most importantly, it is necessary for life. Studies on both rats and Drosophila revealed that sleep loss lasting for too long ends up in death [18,25].

A healthy individual should spend approximately one-third of their day sleeping, stressing the importance of the process. The requisite sleep quality and quantity can change, but there is no specific boundary concerning sleep duration. This parameter varies both intra- and interindividually; thus, many factors determine the required amount of sleep. The American Academy of Sleep Medicine and Sleep Research Society, in their recent recommendation [26], achieved a consensus and established the minimum sleep duration for a healthy adult as 7 hours, although there may be individual variation. However, some studies [27,28] revealed that excessive sleep time might have detrimental health effects, such as increased cardiovascular mortality (concerning older adults). Short sleep duration can

also have a negative health impact; for example, it increases the risk of hypertension [29]. Regarding this, sleep function may change because of aging. For example, many older adults commonly consider themselves to be less drowsy than young adults [30]. In contrast, sleep superficiality and fragmentation increase with age [31]. For many older adults, it takes longer to fall asleep, and the rapid eye movement (REM) phase is shorter, but the nREM phases 1 and 2 lengthen. Moreover, electroencephalogram (EEG) spectral power is lower in older adults [31].

Studies have shown that, besides age, sex is an important factor influencing the quantity of sleep [13,21,32]. The total sleep time among women is typically longer than that in men. Moreover, sleep efficiency (examined by polysomnography [PSG]) is higher in men than in women. Men are known to sleep lighter and get aroused more frequently. However, anecdotally, women report sleep disturbances more often [32].

Sleep and Circadian Rhythms Assessment Methods

Sleep or circadian rhythms (CRs) can be examined using subjective and objective methods. The first method includes questionnaires. Examples of commonly used validated scales include the Pittsburgh Sleep Quality Index (PSQI) for assessing sleep quality measurement and the Morningness-Eveningness Questionnaire (MEQ) for measuring chronotype. Both are designed as self-assessment questionnaires [33-35]. PSQI distinguishes *good* and *poor* sleepers. It comprises 19 questions related to sleep quality, including latency, duration, or any sleep-related problems. The scale is divided into seven components. Each component can be rated from 0 to 3, and the total score ranges from 0 to 21. The higher the score, the more severe the sleep problem [33-35]. In contrast, MEQ is most frequently used for classifying morningness-eveningness types [36]. The MEQ categorizes patients into 5 groups, which differ depending on their chronotype [34]. The chronotype indicates an individual's CR, which manifests itself as sleep-wake preferences. On the basis of 19 self-assessed questions, the scale distinguishes a definitely morning type, a moderately morning type, a neither or intermediate type, a moderately evening type, and a definitely evening type. Generally, morning types prefer to go to bed early and wake up early. However, if evening types wake up early, they would feel tired and are likely to get up with difficulty but are also more likely to fall asleep late in the night [37].

Actigraphy is another tool frequently used to objectively evaluate the sleep-wake parameters. The American Academy of Sleep Medicine recommends its use for examining people with sleep-wake disorders or sleep-disordered breathing [38]. An actigraph is a noninvasive wristwatch-like device that can measure rest-activity data from patients based on movements, and the data can then be analyzed by a software algorithm. However, this method could lead to an overestimation of sleep time and the number of awakenings [39]. In actigraphy, the sleep period is determined at the beginning of the immobility period, but it might not be the exact start of sleep. Nevertheless, actigraphy, if compared with PSG, is more convenient and shows a high accuracy (>80%) [40]; thus, it can be used as an alternative to PSG.

PSG, however, is commonly used as the gold standard for sleep examinations. If multiple channels are available, PSG can be coupled with EEG, electrooculogram, electromyogram, electrocardiogram, airflow, and oxygen saturation. Using PSG, every sleep phase could be distinguished and examined. An individual, when examined with EEG, electrooculogram, and electromyogram, presents three states: vigilance, nREM, and REM sleep [41-43]. One sleep cycle generally lasts between 90 and 110 minutes and is composed of a sequence of different sleep phases [44]. During nREM sleep, four stages are distinguished, in which the latter two stages are the deepest and are called slow-wave sleep. In one night, one could have multiple sleep cycles, but as the night progresses, shorter nREM episodes occur [45]. In one sleep cycle, the nREM phase lasts for 68-90 minutes (overall 75%-80% of night sleep), whereas REM sleep lasts for 5-30 minutes. Following a REM state, one will either turn into nREM state or wake up [46,47]. During the first cycle, REM sleep may last from 1 to 5 minutes; however, REM sleep episodes become progressively longer throughout the night [48].

Neurochemical Modulation of Sleep

Sleep modulation and CR depend on a variety of factors. These concern both neuroanatomical structures (mainly suprachiasmatic nucleus [SCN]) and sleep-modulatory molecules (such as gamma amino butyric acid [GABA], adenosine, acetylcholine, and serotonin) [41] as well as external factors (eg, light and noise) [49]. All of the above participate in the two best-known mechanisms for controlling sleep, that is, a homeostatic and a circadian one. The first one is associated with increasing drowsiness after prolonged wakefulness, whereas the latter promotes wakefulness during the day and sleep at night. The circadian sleep process is based on the function of the SCN, located in the anterior hypothalamus, which receives information from the retina about light exposure and passes it to peripheral receptors via the neuroendocrine system, which will be described later [50]. Signaling in this region provokes vigilance, whereas loss of function causes fatigue and sleepiness [51].

SCN releases the neurotransmitter GABA, which promotes sleep [52,53]. However, the signal from SCN is not the only one needed to trigger nREM sleep. Falling asleep is also a consequence of the aforementioned homeostatic mechanism and adenosine build-up in the brain. Adenosine is a hypnogenic factor that progressively accumulates during wakefulness [42,43]. Moreover, some studies have suggested its importance in triggering nREM sleep by activating sleep-promoting neurons in the ventrolateral preoptic nucleus [43]. Neurons in the ventrolateral preoptic nucleus produce GABA and galanin, which inhibit arousal neurons in the hypothalamus and brainstem [52,54]. Switching from nREM to REM sleep is induced by acetylcholinergic neurons in the brainstem (located in the pedunculopontine tegmental and laterodorsal tegmental nuclei) as well as by GABA, serotonin, norepinephrine, and nitric oxide within this region [52].

Therefore, GABA plays a key role in sleep promotion. The level of GABA is increased during both nREM and REM sleep in comparison with waking values [53,55]. In contrast,

acetylcholine concentration is higher in REM sleep than in nREM sleep and wakefulness [52]. In addition, various monoamines (eg, noradrenaline, dopamine, and serotonin) are also involved in sleep-wake cycle modulation. These molecules protect CR from unwanted changes. Not only the levels of molecules but also the expression of receptors that they bind to fluctuate within CR [49]. The activity of noradrenergic neurons in the locus coeruleus and serotoninergic neurons in the raphe nuclei decreases during nREM and even more during REM sleep [47].

Endocrine Control of Sleep

The rhythmic secretion of most hormonal factors is governed by the internal biological clock and sleep state. Hormones can be divided into sleep-dependent hormones, such as growth hormone, prolactin, thyroid-stimulating hormone, and renin, or determined by CR-dependent hormones such as adrenocorticotropic hormone (ACTH), cortisol, and melatonin [56]. Interestingly, the SCN, which is called *the clock of the brain*, contains receptors for sex hormones [57].

In utero, gonadal embryogenesis occurs through certain genes (eg, *SRY*, *SF1*, *SOX1*, and *DAX1*). Between 10 and 20 weeks, in males, human chorionic gonadotropin is mainly responsible for testosterone production by Leydig cells [58]. This hormone leads to the differentiation of the Wolffian ducts to form the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts. At approximately 8 weeks of pregnancy, the male fetus's Sertoli cells start to produce Müllerian inhibiting substance, which leads to atrophy of the Müllerian ducts. The absence of Müllerian inhibiting substance and testosterone causes sexual differentiation in women. Female sexual differentiation appears to occur without hormonal stimulation [59].

In adults, the plasma levels of various hormones vary according to the sleep stage or CR [56]. The hypothalamic-pituitary-adrenal axis controls the production and secretion of ACTH. The hypothalamus produces a corticotropin-releasing hormone, which stimulates the anterior pituitary to release ACTH. ACTH acts on the adrenal cortex and affects cortisol and adrenal androgen levels. The increase in cortisol provides a negative feedback loop to the hypothalamus, and consequently, the level of corticotropin-releasing hormone decreases [60]. Sleep onset is associated with decreased cortisol secretion. With increasing hours of sleep, there is an elevation of cortisol levels, which subsequently decreases throughout the day after awakening [56].

The gonadotrophin-releasing hormone is synthesized in neurons within the hypothalamus. Its main function is to stimulate the anterior pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [61]. In females, the menstrual cycle is divided into follicular and luteal phases. The former begins on the first day of menstruation. At the beginning of this phase, the ovary secretes a small amount of hormones that leads to low estradiol and progesterone levels. In the midfollicular phase, FSH starts to increase and stimulates the secretion of estradiol. Eventually, the increase in estradiol levels leads to a negative feedback loop. Estradiol peaks one day before ovulation. At this time, a unique endocrine phenomenon occurs as a switch from negative feedback to positive feedback, resulting in a midcycle surge. There is an increase in LH, as well as FSH, but in the case of FSH, the increase is not as high. Progesterone is then released by the corpus luteum. This hormone is responsible for increasing the temperature and relaxing the uterine smooth muscle. Later in the luteal phase, if the oocyte is not fertilized, LH, progesterone, and estradiol levels will decrease. However, estradiol is important for developing secondary sex characteristics in women. It has been suggested that low estrogen level has serious implications such as cardiovascular responsiveness, insulin resistance, and obesity [61].

In males, LH binds to receptors on Leydig cells and stimulates them to produce testosterone. In contrast, FSH acts on Sertoli cells to help promote spermatogenesis. Testosterone can be further converted into two forms: estradiol or 5α-dihydrotestosterone. Its production is implicated in the development of the male phenotype in embryos, providing sexual maturity at puberty and sexual function. In addition, both testosterone and estradiol inhibit the release of gonadotrophin-releasing hormone by the process of negative feedback [61]. In summary, in males, LH is responsible for testosterone production by the testes, and FSH stimulation is important for normal spermatogenesis.

In females, LH and FSH stimulate ovarian production of estradiol and progesterone, which have an impact on sleep changes during the menstrual cycle. There is a pulsatile rise in their levels at sleep onset in both sexes. During prepuberty and puberty, their levels increase during sleep. In addition, hormonal fluctuations during the menstrual cycle have an impact on sleep, for example, by decreasing the REM stage in the luteal phase and increasing sleep stage 2 in the midluteal phase [56]. There is a significant decrease in sleep efficiency and sleep quality as well as an increase in sleep onset latency during the luteal phase.

The association between reproductive hormones and sleep has been studied previously; however, further research is needed. One evidence comes from the fact that hormonal profiles vary between sexes, and there are several sex differences in sleep patterns. Women generally need more sleep, spend more time in bed, and sleep longer. They also report more sleep difficulties, but by actigraphy, women have better sleep quality compared with men [56]. Furthermore, recent studies have shown that sex hormones have different impacts on CR and sleep physiology in males and females. In female rats, estradiol promotes arousal in the active phase of sleep, but after sleep loss, both estradiol and progesterone selectively facilitate REM rebound while reducing nREM intensity [62]. A similar effect of estradiol in facilitating REM rebound has also been shown in castrated male rats [63]. However, testosterone influences the organization of CR and the timing of sleep. For example, in young men, higher baseline testosterone levels are associated with the evening chronotype [64]. It is also believed that testosterone concentration decreases during the day and peaks after 90 minutes of sleep in the evening, coinciding with the first REM phase of sleep [65]. In a cross-sectional analysis, no association was found between serum levels of various hormones (free testosterone, bioavailable testosterone, total testosterone, and sex hormone–binding globulin) and sleep quality [66]. However,

impaired sleep and elevated BMI were associated with low testosterone levels in a study of 9756 men aged 16-80 years [67].

Several studies have explored the relationship between sleep and reproductive hormone secretion [68-70]. In one such study, a significant association was found between FSH levels and sleep duration in women with normal cycles. FSH levels were 20% higher in long-time sleepers than in short-time sleepers [71].

Genetic Basis of Sleep and CRs

Various genes may also influence sleep and CR. For example, CR relies on the functioning of the *CLOCK:BMAL1 (*brain and muscle ARNT-Like 1*)* complex and the expression of genes such as CLOCK (*circadian locomotor output cycles kaput*), *PER* (*period*), *CRY* (*cryptochrome*), and *TIM* (*timeless*). The *CLOCK:BMAL1* complex is formed by two positive regulators. They bind to the DNA during the day to promote *PER* and *CRY* expression. In the evening, PER combines with CRY in the cytoplasm, then migrates to the nucleus and subsequently inhibits *CLOCK:BMAL1* and, in turn, its own transcription. Afterward, the heterodimer PER/CRY disintegrates; thus, *CLOCK:BMAL1* is not repressed. This cycle is called a transcription/translation feedback loop, which is repeated every 24 hours [50,72,73]. Of note, the expression of the PER/CRY complex is not the only process regulated by *CLOCK:BMAL1* [50,73]; however, it is the core one that modulates CR [50].

The exact roles of the aforementioned gene products are still not well defined. However, studies have shown that PER plays an important role in maintaining appropriate circadian timing [50]. *PER3* gene polymorphism affects sleep homeostasis, and pathological loss of *the PER1 and PER2* genes in mice leads to increased sleep pressure [74]. Furthermore, the four-repeat *PER3* allele, compared with the five-repeat allele, is associated with decreased slow-wave sleep and better cognitive performance after sleep deprivation [75]. In addition, the double knockout of *CRY1-2* in mice results in an increased nREM sleep phase and complete dysregulation of CR. Moreover, an insufficient *CLOCK* gene disrupts CR in mice under constant darkness [74]. However, full knockdown of *TIM* causes death in mammalian fetuses, and conditional knockdown promotes circadian arrhythmicity in the SCN [76,77]. Mutations in any of the *PER*, *CRY*, or *TIM* genes are considered to cause familial advanced sleep phase syndrome, in which patients wake up and go to bed early, therefore presenting features of morning chronotype [78].

In peripheral blood, products of circadian genes expression can be found at a concentration similar to that of SCN (obtained from mononuclear cells).

miRNAs and Circadian Clock

Epigenetics provides new insights into the circadian clock. The commonly known types of epigenetic changes involve the expression of noncoding RNAs, such as circulating miRNAs [79,80]. The following miRNAs may have an important role in altering CR: miR - 132, miR - 219, miR - 192, miR - 194, and miR-34a [81-83]. Studies of rodents have shown that levels of miR - 132 are associated with light - dependent resetting of the circadian clock, and miR - 219 was shown to maintain the length of the circadian period [81]. In addition, miR - 192 and miR - 194 (miR - 192/194) are powerful regulators of PER family members (*PER1*, *PER2*, and *PER3*) [83]. The overexpression of these miRNAs may inhibit the synthesis of PER proteins, resulting in an altered CR [83]. In addition, overexpression of miR-34a is associated with a decrease in the synthesis of PER1 protein [82].

Body Composition and Sleep Quality

Due to the global obesity problem, an understanding of the factors significantly related to body weight and composition is needed. Obesity is currently one of the most common causes of health problems in developed countries, including Poland, New Zealand, Japan, and the United Kingdom [84]. According to the latest results of the European Health Interview Survey, people in Poland who are overweight and obese constitute 37.5% and 17.2% of the total population aged ≥18 years, respectively. These results were above the average for the 28 European Union countries, which is 35.7% of people who are overweight and 15% of people with obesity [85].

A variety of factors, such as physical activity, exposure to stress, and eating habits as well as sleep quality, may affect body composition. Sleep is an essential element in the regeneration of the body and provides appropriate management of energy resources [86]. Short sleep leads to more frequent use of stimulants, which is also associated with the deposition of more fatty acids [87]. People with poor quality of sleep are more likely to have more body fat and a predisposition to obesity [88]. In addition, people who sleep less also tend to accumulate adipose tissue [89]. The DR (2D:4D) is commonly linked with body components, especially muscle body content [90] and fat tissue [91]. Higher PAE, as indicated by a lower DR, is associated with a higher content of muscle tissue among adult men [92] and children [93]. In addition, a higher DR (indicative of lower PAE) is associated with excess body fat, independent of the stage of life [93,94].

Sleep and Sexual Function

Another goal of this study is to explore the association between sleep quality and sexual function. Sleep problems are common in many populations [95,96], which may reflect daily lifestyles. People may experience acute sleep loss in a single night, but chronic sleep deprivation, where people have inadequate sleep over several consecutive days, can also occur. Chronic sleep deprivation can detrimentally affect health by increasing the wear and tear of various body systems (ie, the allostatic load) from repeated consecutive sleep loss [97]. This cumulative stress can negatively affect metabolic, immune, and psychological health [97,98].

Sexual inactivity is also becoming common in some societies [99,100]; however, few studies have explored the relationship between sleep quality and sexual function. Given that the main brain center for male sexual behavior (ie, the preoptic area [101]) is also a sleep-promoting area [102,103], there is a possible biological link between these two functions.

Several preclinical studies have explored the impact of sleep deprivation on male sexual behavior. However, these studies

mainly used the same sleep deprivation paradigm (ie, 96 hours of REM sleep deprivation). The findings from these studies were inconsistent, including no effect [104,105], impairment [106,107], and even improvement [108] of male sexual behavior. Interestingly, the earliest study on the effect of REM sleep deprivation on male sexual behavior found that rats that were *low* copulators exhibited an increase in their sexual activity following a week of REM sleep deprivation [109]. Unfortunately, the data from that study were only published as an abstract, so the experimental details were not reported. Recently, one of the authors (EW) found that daily mating sessions for 2 weeks dampened sexual behavior in male rats. However, the muted sexual response lasted longer in rats that were chronically sleep deprived (kept awake for 4 hours per day for 1 week) [110].

Human studies have also documented an association between sleep deprivation and impaired sexual function. For example, Seehuus and Pigeon [111] found an association between insomnia symptoms with lower intercourse satisfaction in males as well as with sexual arousal and vaginal lubrication in females. In addition, Kalejaiye et al [112] showed that men with obstructive sleep apnea reported worse erectile function than those without the condition. Furthermore, a recent study found bidirectional associations between insomnia symptoms and orgasm difficulty [113]. The analyses in that study were controlled for age, number of comorbidities, BMI, past use of androgen deprivation therapy, daytime sleepiness, fatigue, and depressive and anxiety symptoms. Furthermore, obstructive sleep apnea has been associated with erectile dysfunction in men, and the use of continuous positive airway pressure, which improves sleep quality, may improve erectile function [114].

Currently, however, there is little information on how objective sleep parameters (eg, sleep stages, sleep or wake latencies, and number of awakenings) are linked to sexual function in healthy populations. However, determining this would have clinical relevance as it may help indicate which sleep-related outcomes need to be improved to increase sexual function.

In this study, we will conduct both subjective and objective assessments of sleep as well as collect sexual function data using validated questionnaires, with the aim of finding associations between sleep and sexual parameters. Subjective sleep quality will be measured using the PSQI [33]. Objective sleep measurement will be performed using a portable PSG system (Nox 1A, ResMed), which can monitor various sleep parameters, including total sleep time and duration of REM and nREM phases. In addition, we will include an MEQ [115] to help indicate participants' chronotype (ie, whether one is more of a *morning* or *evening* person), as people with sleep problems are less likely to be a *morning* person [116-119].

Sexual function will be assessed using the Arizona Sexual Experience Scale, which is a brief five-item scale measuring self-reported information on the strength of sex drive, how easy it is to be sexually aroused, to get and maintain an erection, to reach an orgasm, and orgasm satisfaction [120].

DR and Sexuality

Some data support the Organizational and Activational Hypothesis on human sexuality, but these studies have limitations. For example, the majority (93%) of 46XY individuals with androgen insensitivity syndrome are androphilic, that is, attracted to men [121]. Additional evidence comes from women with congenital adrenal hyperplasia who have higher levels of androgens than normal and a higher likelihood for same-sex attraction than women without the condition [122]. This suggests that androgens play a role in gynephilia, that is, attraction to women. However, these data should be considered with caution. For example, the study by Wisniewski et al [121] had a small sample size of 14, and in the study by Meyer-Bahlburg et al [122], not all women with congenital adrenal hyperplasia had a sexual attraction toward women.

Many studies have explored the association between DR and sexual orientation. Breedlove and his team [123] were the first to conduct such a study, where it was found that the DR of the right hand in gynephilic women was smaller than that of androphilic women, but the study reported no such difference between androphilic and gynephilic men. Since then, several studies have explored similar associations in both sexes, and the review by Grimbos et al [124] found that androphilic women, on average, have larger (ie, more female typical) DRs than gynephilic women. This finding suggests that the attraction to females in gynephilic women may be mediated, at least partially, by exposure to elevated levels of prenatal androgens. However, the data for males are less consistent [125-130]. It is still worth noting, though, that some studies have found that heterosexual men have a smaller DR on average than homosexual men [125-127,130]. Again, this may suggest that the androphilic attraction in males may be attributed, at least partially, to lower PAE.

Overall, studies on the relationship between DR and sexual orientation remain controversial [123,131,132]. This is not surprising, as biological studies on sexual orientation could potentially be political [133], with some people of the view that sexual orientation is predominantly socially determined rather than biologically based. We recognize that all theories on the biological basis of sexual orientation have caveats. However, a controversial topic should not stop researchers from further investigations in this area. Indeed, further studies are crucial to provide evidence, be it biological or social, in an objective way.

Several factors have been discussed regarding the limitations of assessing DR. One aspect, which is often noted, is the fact that the effect size is not large, and there is no cut-off indicating male or female pattern of DR; thus, there is a large overlap in the distribution of DR between sexes. This is also true for studies exploring differences in DRs of people with various sexual orientations. In addition, many studies that attempted to find an association between DR and sexual orientation have collected DR data through indirect methods, such as from photocopies or scans. However, it is now known that there is a potential discrepancy between direct and indirect measurements of DR [134]. Furthermore, these studies explored the relationship between sexual orientation and biological but nonbiological

factors, such as social factors, which some researchers have suggested to play a role in sexual orientation [133], were not accounted in those studies.

In addition, studies on sexual orientation and DR have rarely considered two important factors: (1) handedness and (2) sexual attraction (how attracted one is to the same and opposite sex) *per se* rather than sexual identity (eg, gay, bisexual, and heterosexual). It is important to consider handedness, as nonheterosexual populations are more likely to be non–right-handed [135]. However, studies often only analyze data based on the left or right hand. Regarding sexual attraction, studies have often analyzed data based on sexual identity (eg, heterosexual, homosexual, and bisexual). These categories can be subjective. Considering that DR is a continuous variable, researchers need to consider DR data based on the degree of sexual attraction (ie, how much attraction one has toward the opposite sex and the same sex). The Kinsey Scale, which was originally used to determine the degree of sexual activity with the opposite and same sex, could potentially be adapted for a degree of sexual attraction. In this study, we aim to better understand the association between PAE (indicated by DR) and sexual attraction (not sexual identity) by taking into account the participants' handedness information.

Finally, we are not aware of any previous or pending studies that have associated DR with sexual function *per se* (eg, sexual desire, erectile function, and orgasm). Therefore, we will investigate this topic as well. This will help indicate the extent to which PAE plays a role in determining sexual function in adulthood.

Objectives

Objective 1

We will explore the association between PAE as indicated by the DR and sleep function in young adults. This research will have two phases to address this objective. In phase 1, sleep parameters will be assessed using a validated questionnaire (subjective measure). In phase 2, we will determine if PAE is related to objective sleep measures (using actigraphy and portable PSG), along with sleep-related correlates such as hormones, circadian regulatory proteins, and body composition.

Objective 2

Here, we will explore if sleep quality is associated with sexual functions. We will collect both objective and subjective sleep parameters. Sexual function data will be assessed using validated questionnaires. In addition, as noted above, we will investigate the extent of how PAE is associated with sexual function in young adults.

Objective 3

Finally, we will determine the association between PAE (indicated by DR) and sexual attraction, while taking into account the participants' handedness information. Our finding may help show whether handedness information (which is associated with hormones and brain lateralization) can help explain the inconsistencies in past findings of DR and sexual orientation studies.

Methods

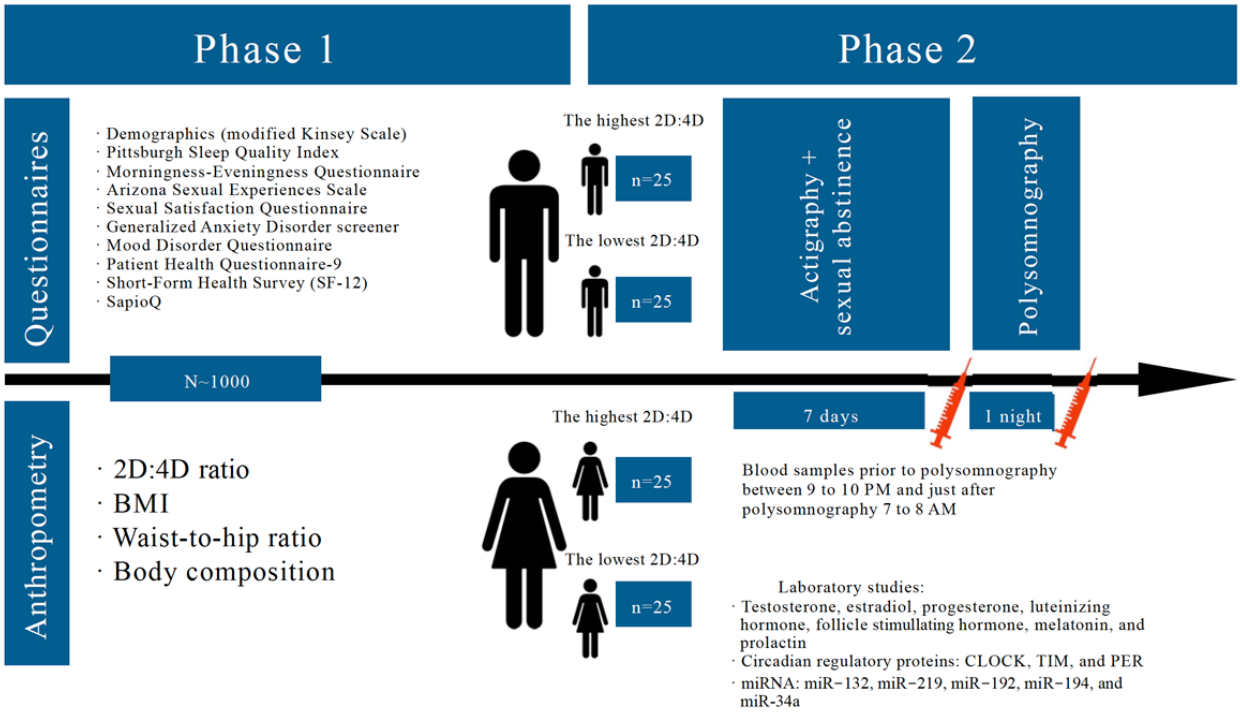
Recruitment

This research will be undertaken in two phases, with parallel recruitments in 4 different countries. Five institutions (Medical University of Lodz, Poland; University of Lodz, Poland; University of Otago, New Zealand; Aichi Medical University, Japan; and Swansea University, United Kingdom) are participating in this study.

Phase 1

As shown on Figure 1, in phase 1, we plan to recruit at least 1000 participants from each site. Eligibility criteria are listed in Textbox 1. The large sample is required because of the third aim, where we intend to recruit participants from sexual minorities (ie, gay, bisexual, and lesbian), which can be challenging. In one study [22], about 150 participants per group were sufficient to detect a significant difference of approximately 10% in the DR of heterosexual and nonheterosexual people. In a recent survey at the University of Otago [136], approximately 28% (356/1234) of students were identified as sexual minority. If 30% of our participants are sexual minority, that would be approximately 300 participants (150 male and 150 female) out of 1000.

Figure 1. Flowchart of the study. CLOCK: circadian locomotor output cycles kaput; PER: period; TIM: timeless; 2D:4D ratio: ratio of the second digit length to the fourth digit length.



Textbox 1. Inclusion and exclusion criteria.

Inclusion Criteria

- A full understanding of the study rules by the participant was confirmed by written informed consent to participate in the study
- Age range: 18-30 years

Exclusion Criteria

- Diagnosis of chronic, hormonal, and mental health conditions
- Pregnancy and lactation
- Taking long-term medicines (including hormonal contraception)
- Injuries to the fingers of the upper limbs
- Deformation of the fingers of the upper limbs
- Diseases leading to deformation of the fingers of the upper limbs
- Lack of consent or inability to follow recommendations related to participation in the study

Upon consenting, participants will need to do the following:

1. Complete questionnaires on demographics (eg, age, ethnicity, sex, gender, sexual attraction using the Kinsey Scale, sexual orientation, and handedness); PSQI; MEQ; Arizona Sexual Experience Scale; Sexual Satisfaction Scale; Generalized Anxiety Disorder screener; Mood Disorder Questionnaire; Patient Health Questionnaire-9, short-form health survey; and SapioQ.
2. Have anthropometric measurements (body weight, height, BMI, finger length: index and ring fingers, waist, hips, and neck circumference) recorded.
3. Body composition analysis (InBody 270) will be used to determine fat and muscle mass. We include this analysis because obesity is linked to sleep-related breathing disorders as well as insomnia. Noninvasive, easy, and common body impedance analysis method is based on measuring the electrical impedance in various body tissues, that is, the sum of geometric resistance (active resistance) and reactance (passive resistance). Bioelectrical impedance analysis is used to assess the values of the body components, such as fat-free mass (%), fat mass (%), muscle mass (%), and total body water (%). In addition, segmental lean and fat distribution can be measured to assess tissue distribution in each quarter of the body. The basic metabolic rate is calculated. Before each measurement, foot, feet, and hands must be wiped using wet wipes to increase electrical conductivity. During the measurement, the individual should be in an upright position [137].

Phase 2

Overview

When phase 1 is completed, we will follow up with those interested in phase 2. For this phase, we estimate that we will need at least 50 male and 50 female participants, regardless of sexual orientation. Using reference data from the PSQI, we estimate that, for each sex, we will need 25 participants with DR<1.0 (indicative of high PAE) and 25 participants with DR>1.0 (indicative of low PAE) to detect a 50% difference in sleep quality, with an α level of .05 and a power of 0.8.

Once consented, each participant will need to do the following:

1. A 1-week quantitative daily and nocturnal activity recording using portable actigraphy. On the basis of the actigraphic record, it will be possible to evaluate parameters such as the average level of activity during the day and at night, the amount of time spent actively and inactively during the day and night, average sleep time, sleep continuity, number of awakenings during sleep, and number of naps during the day. On the last day, one-night PSG data (total sleep time, duration of REM and nREM phases, apnea-hypopnea index, arousal index, and saturation) will be captured with a Nox A1 (ResMed). During 1-week actigraphy, all participants will have to agree to sexual abstinence because of blood samples before and just after PSG.
2. Blood collection, before and after the polysomnographic night for assessment of various hormones (testosterone, estrogen, estradiol, progesterone, LH, FSH, and prolactin) and circadian regulatory proteins (eg, CLOCK, PER, and TIM) as well as selected miRNAs.

Enzyme-Linked Immunosorbent Assay

The levels of the investigated proteins will be assessed using enzyme-linked immunosorbent assay kits. Each assay will include six standard concentrations, and every sample will be run in duplicate. The concentration will be assessed using a microplate reader to measure the absorbance at 450 nm. The standard curves will be created using the four-parameter logistic method. All samples should be within the assay range in accordance with the information supplied by the kit manufacturer. An interassay coefficient of variation of less than 15% is acceptable. The intra-assay coefficient of variation values were less than 10%.

miRNA

The common miRNA procedure includes the following steps: RNA isolation, reverse transcription, and quantitative polymerase chain reaction using appropriate starters for each miRNA. An RNA/miRNA purification kit is needed to isolate miRNAs. A reverse transcription kit was used to perform reverse transcription. The analyses will be performed according to the protocol supplied by the manufacturer, using an appropriate amount of RNA in each sample. The reactions will be performed in a thermocycler according to the reaction parameters supplied by the manufacturer. Furthermore, we will dilute the obtained cDNA according to a protocol using RNAse-free and DNAse-free water. The final step will be quantitative polymerase chain reaction analysis for each sample in duplicate and each miRNA (using proper starters) using a real-time polymerase chain reaction machine. The obtained results will be analyzed using the software that calculated the cycle threshold (Ct) for each sample. The samples over Ct=39 cycles will be excluded from further analyses. The spike in the kit is used to normalize the expression levels of the obtained miRNAs. The delta cycle Ct method will be used to make a final calculation using the following formula: 2(mean CtmiR − mean Ct of reference) [138].

Data Analyses

Demographic data will be summarized with descriptive statistics.

Objective 1

Subjective sleep measures and sexual data from phase 1 as well as objective sleep measures and its (hormonal, molecular, and psychological) correlates from phase 2 will be compared between participants with DRs<1.0 (indicative of high PAE) and participants with DR>1.0 (indicative of low PAE) for each biological sex, while taking into account their handedness.

Objective 2

Multiple regression analyses will be performed to determine the relationship between sleep and sexual parameters while controlling for age, BMI, psychological health (anxiety and depression), chronotype, and sexual orientation.

Objective 3

For each sex, DR data will be categorized by handedness and correlated with sexual attraction (measured using the Kinsey Scale).

Results

In 2020, we started the first and second stages of our study in Poland. In phase 1, we recruited 720 participants, of whom 140 underwent anthropometric measurements. The second stage started in February 2021, and since then, 25 participants have completed the data collection for phase 2. We expect to complete the data collection for phase 2 in 2022.

Discussion

Data from this study will provide some information on how PAE is associated with sleep and sexual functions as well as sexual attraction. Many factors may contribute to sleep and sexual problems. However, our research should provide further insight from a biological perspective on how early-life hormonal factors can have a long-term impact on these functions. Furthermore, we will obtain information on the role of PAE in sexual attraction.

Acknowledgments

This study is conducted in accordance with the amended Declaration of Helsinki, and the Ethics Committee of the Medical University of Lodz approved the study protocol (RNN/394/19/KE); Miniatura 4, National Science Centre—no 2020/04/X/NZ4/00564.

Authors' Contributions

The contribution of WK and EW is equivalent and accounts for 80% of the contribution to this research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the National Science Centre, Poland.
[PDF File (Adobe PDF File), 100 KB - resprot_v10i10e29199_app1.pdf]

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Abbreviations

ACTH: adrenocorticotropic hormone
BMAL1: brain and muscle ARNT-Like 1

CLOCK: circadian locomotor output cycles kaput
CR: circadian rhythm
Ct: cycle threshold
DR: digit ratio
EEG: electroencephalogram
FSH: follicle-stimulating hormone
GABA: gamma amino butyric acid
LH: luteinizing hormone
MEQ: Morningness-Eveningness Questionnaire
nREM: nonrapid eye movement
PAE: prenatal androgen exposure
PER: period
PSG: polysomnography
PSQI: Pittsburgh Sleep Quality Index
REM: rapid eye movement
SCN: suprachiasmatic nucleus
TIM: timeless

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Protocol

An Advanced Nursing Directive for Children With Suspected Appendicitis: Protocol for a Quality Improvement Feasibility Study

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Abstract

Background: Pediatric appendicitis accounts for an estimated 7% to 10% of abdominal pain cases in the emergency department (ED). The diagnosis is time-consuming, and the investigative process depends on physician assessment, resulting in delays in diagnosis and therapeutic management. The utility of an advanced nursing directive (AND) to expedite this process is unclear and needs further exploration.

Objective: This study aims to describe key components of ED flow in patients with suspected appendicitis seen at a pediatric ED and pilot a directive that allows ED nurses to perform an order set that includes blood work, urine tests, analgesics, fluids, and an abdominal-pelvis ultrasound prior to physician assessment.

Methods: This study involves conducting a retrospective chart review alongside a quality improvement initiative to compare key ED flow metrics before and after AND implementation. Primary outcome measures include median time from ED triage assessment to ultrasound completion, analgesia administration, blood work results, and time to disposition (consult or discharge), alongside other key ED flow metrics for suspected appendicitis. Secondary outcomes will involve patient and caretaker satisfaction surveys. Descriptive statistics will be used to summarize the data. For differences in proportions, a chi-square test will be used. The Student *t* test will be used for continuous variables. A variable-controlled run chart will be performed to assess impact on ED flow metrics. Patient and family satisfaction surveys are administered immediately after the directive encounter and 7 days afterward.

Results: There are currently 3900 patients who have been screened, 344 patients who have been enrolled, and 90 patients who have received the medical directive since implementation in June 2020. Interim results on reduction of time to diagnostic and therapeutic ED flow parameters and satisfaction surveys are expected to be published in February 2022. The final study endpoint will be in June 2022.

Conclusions: This study proposes a novel protocol for improving the diagnosis and treatment of suspected pediatric appendicitis through implementation of an evidence-based AND. This model may provide a standardized, international pathway for management of common pediatric and adult emergencies.

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KEYWORDS

quality improvement; pediatric; nursing; medical directive; appendicitis; emergency department flow; nursing directive

Introduction

Background

Acute appendicitis is the most common pediatric surgical emergency [1]. This condition, characterized by inflammation of the appendiceal lumen, accounts for an estimated 7% to 10% of all abdominal pain cases presenting to the emergency department (ED) [2,3]. Although the overall incidence of appendicitis may be declining among Canadian children [4], perforated appendicitis, a serious cause of morbidity and mortality, occurs more frequently in children, making early diagnosis and treatment imperative [5,6].

Appendicitis typically presents with a sequence of acute onset colicky pain to the umbilicus, which then becomes sharp and constant and then migrates to the right lower quadrant (RLQ) [1]. Children frequently present with fever, nausea, vomiting, anorexia, and constipation. Although this classic presentation has been shown to vary depending on the age and dietary patterns (such as decreased fiber intake) of the patient in question [7], the diagnosis is predominantly clinical. The final diagnosis is typically made by ED physicians based on clinical judgment as well as a combination of investigations, including urine analysis, pregnancy tests, complete blood count, inflammatory markers, and ultrasound (US) imaging. Clinical decision rules can also be used to streamline the diagnostic workup but rely on the result of white blood cell count and neutrophils or bands as well as clinical features. In addition to blood work, US is a rate-limiting step in the time to diagnosis of appendicitis, as it is often used for patients who present atypically or who are at intermediate risk based on clinical decision rules. After diagnosis, the surgical team is consulted for definitive surgical or medical management [8]. This entire process is lengthy, with one study demonstrating that the average ED length of stay (LOS) was 464 minutes (7.7 hours), the mean time to analgesia was 252 minutes (4.2 hours), the mean time to US performed was 378 minutes (6.3 hours), and the mean time to appendectomy was 717 minutes (12 hours) in Canadian pediatric hospitals [9].

The utility of an advanced nursing directive (AND) allowing nurses to order blood work and imaging studies, such as US, to expedite the diagnostic process of appendicitis remains unclear. ANDs, also commonly referred to as medical directives, serve to empower nursing staff by enabling them to provide advanced levels of care to patients prior to physician assessment, and they have been shown to reduce ED LOS and time to disposition (discharge, consultation, or admission) [10]. Prior studies have examined nursing-initiated therapeutics, including therapies for asthma [11,12], pulled elbow reductions [13], radiograph ordering for suspected fractures [14], and oral rehydration pathways for gastroenteritis [15]. One meta-analysis of four studies investigating a clinical decision rule that allowed nurses to order ankle radiographs showed that there were significantly fewer x-rays (odds ratio 0.36, 95% CI 0.22-0.59) with no difference in proportions of positive ankle fracture x-rays or missed fractures, as well as a 35-minute reduction in ED LOS when comparing the triage nurses using this clinical decision rule to physicians [16]. For therapeutic interventions, ANDs have been shown to reduce the time to analgesia by an average of 30 minutes, which resulted in significant reductions in pain scores and increases in patient satisfaction rates [17].

Initial research has shown the strong potential of ANDs to expedite and improve the quality of patient care in the ED without increasing ED resource use for various conditions. However, there is a lack of research exploring the utility of an AND for the workup of children with suspected appendicitis. Thompson et al [18] have shown that ANDs that empower nurses to begin investigations prior to physician assessment have resulted in a significant reduction in time of triage to blood draw, hospital admission, and surgical appendectomy. However, the AND used in this study did not allow nurses to order imaging studies in cases of suspected appendicitis, resulting in no reported difference in time to US between groups. As this is a key investigation in confirming the diagnosis, it is essential to determine if expediting time to US can also improve patient outcomes and ED flow metrics.

Aims and Objectives

To build on the early work by Thompson et al [18], we have designed a novel AND that allows nurses in our ED to order imaging studies in patients with suspected appendicitis. Our primary goal with the implementation of this novel AND is to reduce ED LOS and time to disposition for patients presenting with suspected appendicitis by 20% from baseline. Our secondary goals are to decrease time to other key steps in the diagnostic and therapeutic management of patients with suspected appendicitis, including times to initiating blood work, fluid filling of bladder, and analgesia. Moreover, through the implementation of this AND, we aim to improve the satisfaction levels of both patients with suspected appendicitis and caregivers when presenting to the ED.

Methods

Study Design

The implementation of this novel AND was designed as a quality improvement (QI) initiative. Data will be collected to compare the outcomes of a standard of care (SOC) group against a group of patients that received the AND. The protocol for this study was approved by the Hamilton Integrated Research Ethics Board.

Development of the AND

This novel AND was designed in collaboration with physicians, allied health care workers, members of our institution's family council, and hospital management leaders. This project was developed to build on a prior successful appendicitis QI project from our institution [19], which was a clinical pathway that assisted physicians in risk stratification of patients with suspected appendicitis after US completion to expedite disposition.

We reviewed previously validated appendicitis scoring systems and, via group consensus, chose to base our directive off the pediatric appendicitis score (PAS) [20]. This screening tool is simple, and when used in a clinical pathway that includes advanced imaging such as US, there is a high sensitivity and

specificity (92% and 95%, respectively), a positive likelihood ratio of 17.3, and a negative likelihood ratio of 0.08 [21]. Our screening tool made slight modifications to the original PAS because nursing assessment at our institution is done prior to laboratory investigations. Criteria such as complete blood count results were not included in our AND (Table 1). According to the PAS, a score of ≥4 is medium risk and will require investigation for appendicitis using laboratory work and US. Patients with RLQ tenderness to cough, percussion, or hopping alongside tenderness on palpation over the RLQ are given a score of 4 (medium risk) on the PAS. Therefore, appendicitis cannot be ruled out without further investigation. For our AND, we included patients who present with abdominal pain and have the above two clinical features.

During the conception of this study, our team wanted to ensure we appropriately addressed the interest and viability of the methods with nursing staff. We sought the input of several nurses and our unit's educational nurse when designing the AND. We surveyed all the nurses in our ED to assess their perceptions of the AND. A total of 52 nurses (full and part-time) were invited to complete the nursing survey regarding their perceptions of the AND. Of the 52 nurses, 39 completed our survey (75% response rate). In total, 85% (33/39) of all nurses were comfortable assessing the abdomen for RLQ pain. The respondents estimated that 85% of the time, there is agreement between nurses and physicians regarding whether a possible appendicitis diagnosis requires further investigation. In addition, 90% (35/39) of respondents thought that the AND would improve patient flow metrics (time to disposition, ED LOS), improve patients' experience, and empower nurses to facilitate patient care.

Table 1. Criteria for the original PAS versus the AND-modified PAS.

Signs and symptoms	PAS[a] criteria	AND[b]-modified PAS criteria for screening eligible patients
RLQ[c] tenderness to cough, percussion, or hopping	No=0 Yes=+2	No=0 Yes=+2
Anorexia	No=0 Yes=+1	N/A[d]
Fever (temperature ≥38 ºC)	No=0 Yes=+1	N/A
Nausea or vomiting	No=0 Yes=+1	N/A
Tenderness over right iliac fossa	No=0 Yes=+2	No=0 Yes=+2
Leukocytosis (WBC[e] >10,000)	No=0 Yes=+1	N/A
Neutrophilia (ANC[f] >7500)	No=0 Yes=+1	N/A
Migration of pain to RLQ	No=0 Yes=+1	N/A

[a]PAS: pediatric appendicitis score.

[b]AND: advanced nursing directive.

[c]RLQ: right lower quadrant.

[d]N/A: not applicable.

[e]WBC: white blood cell.

[f]ANC: absolute neutrophil count.

Eligibility Criteria, Setting, and Sampling

This novel AND will be implemented at our institution that serves a catchment area of 2.3 million people with an annual ED volume of approximately 50,000 patients. After consultation with our institutions' nurses, nurse educator, and family council, we determined that the AND should be applied to children with classic appendicitis symptoms that have minimal comorbidities. The patient eligibility criteria listed in Textbox 1 are required by the bedside nurse to initiate care as directed by the AND.

Textbox 1. Eligibility criteria for patients with suspected appendicitis to receive the AND.

Inclusion criteria

- Age 3–17 years (children ≤2 years of age are at low risk for appendicitis and present atypically [7])
- RLQ abdominal pain with cough, jump, or percussion
- Right iliac fossa tenderness
- Symptoms ≤4 days in duration (longer duration of pain is less likely to be appendicitis [7])

Exclusion criteria

- Prior abdominal surgery, excluding extraperitoneal (eg, inguinal hernia repair)
- Implantable abdominal devices (eg, shunt, dialysis, catheter)
- Any of the following comorbid conditions: diabetes, immunocompromised, sickle cell disease, active rheumatological conditions, active cancer, inflammatory bowel disease, short gut or Hirschsprung disease, or 24-hour trauma diagnosis

Directive Implementation

There are two simultaneous phases to the directive implementation. During phase 1, we ran educational sessions for all nurses and child life specialists on signs and symptoms of appendicitis for screening, and on the components of the PAS and the AND. In the post-implementation period (phase 2), triage nurses screen children who present with chief concerns that are related to appendicitis (abdominal pain, RLQ pain, vomiting, anorexia, acute abdomen, abdominal distension, and abdominal tenderness). If the child meets the inclusion criteria for suspected appendicitis, the patient's chart will be flagged, and they will be prioritized in a room. However, they are to remain in the same order to be seen by the physician, which is determined by the Canadian Triage and Acuity Scale (CTAS) score and time of arrival, so as not to impact the flow of other patients through the ED. Once in a room, the primary nurse completes primary assessment, the AND, and a PAS. For patients with a score of ≥4, an emergency nurse can perform the procedures shown in Figure 1 and Textbox 2 before assessment by an ED physician.

Figure 1. Advanced nursing directive algorithm for children with suspected appendicitis. HCG: human chorionic gonadotropin; IV: intravenous; PAS: pediatric appendicitis score.

Textbox 2. Advanced nursing directive order set.

- Establish intravenous access
- Obtain blood work (complete blood count/differential, electrolyte levels, C-reactive protein)
- Order diagnostic imaging, including abdominal/pelvic ultrasound
- Administer a bolus of 0.9% normal saline at 20 cc/kg, with a maximum of 1 liter to fill bladder for ultrasound (a requirement in our center to displace bowel out of pelvis)
- Offer analgesia consisting of intravenous ketorolac for moderate to severe pain or oral ibuprofen/acetaminophen for mild pain and document whether analgesia was received or declined
- Collect urine from the post-ultrasound void and send for routine urine analysis; send for urine culture if urinalysis is positive for nitrites or leukocytes and order point-of-care pregnancy test (beta-human chorionic gonadotropin) for female adolescent patients (>12 years old)

Patient and Caretaker Satisfaction Survey

We will administer a patient satisfaction survey before and after the implementation of the AND. The survey was adapted from the Emergency Department Patient Experience of Care (EDPEC) survey developed in the United States [22], which is a standardized, valid, and reliable questionnaire to measure adult patients' experience of ED care (see Multimedia Appendices 1 and 2).

Outcome Measures

Primary outcome measures include time to (measured from triage, in minutes) (1) intravenous (IV) catheter insertion, (2) blood work results, (3) analgesia administration, (4) IV fluid completion, (5) US requisition fax time, (6) US completion, (7) US reporting, (8) disposition (time to consult or discharge), and (9) ED LOS. Secondary outcome measures include (1) patient satisfaction (as measured on patient satisfaction surveys) and (2) balancing measures such as the proportions of laboratory tests, urine tests, and US ordered for possible appendicitis before and after the implementation of AND.

Data Collection

To collect data from both the SOC group and the AND group, we will retrospectively screen the charts of patients who meet the inclusion and exclusion criteria outlined above. To do this,

we queried the decision support team at our institution for all pediatric ED visits between April 2018 and June 2020 stratified based on the chief concerns as shown in Figure 1.

A standardized case report form will be used for data collection, including demographics (ie, sex and age), symptoms at the onset of presentation, results of relevant laboratory investigations (ie, complete blood count, electrolytes, beta-human chorionic gonadotropin), relevant imaging results (ie, US results), disposition (ie, home, admission to hospital), treatment modalities (ie, antibiotics, pain medications, surgery), and time to each of the steps in this workup (in minutes) (see Multimedia Appendix 3).

No personal identifiers, such as the patient's name, will be collected or recorded on the study forms. Instead, each participant will be given an enrollment number. Patients from the SOC group will be assigned a screening number beginning with MCH-S and a unique 4-digit code (eg, MCH-S-1234); those who are eligible based on the inclusion and exclusion criteria will receive an enrollment number beginning with the letters MCH-E and ending with a unique 4-digit code (eg, MCH-E-1234). Patients from the AND group will be given an enrollment number beginning with the letters MCH-D and ending with a unique 4-digit code (eg, MCH-D-1234). Two designated research members will then review a proportion of the case report forms at random for completion and discrepancies. Incomplete or discrepant data will be ameliorated by a third independent reviewer.

Data Entry

All study data will be entered into an electronic database, Research Electronic Data Capture (REDCap), by study team members at our institution. The REDCap database will be maintained and accessible only within our institution. All study data will be identified by unique study IDs only, as previously mentioned.

Statistical Analysis

Patient characteristics will be summarized overall and by phase of study to compare before and after implementation of AND. Categorical variables will be summarized using frequencies, proportions, and rates. Continuous variables will be summarized using means, medians, SDs, and IQRs where appropriate. For patient and provider baseline characteristics, chi-square and Fisher exact tests will be used to compare categorical variables, and the Student *t* test or Wilcoxon rank sum test will be used for continuous variables between two phases of the study. Baseline characteristics of patients in the two phases of the study will be tested. In the time-to-event analysis (time to disposition), we will censor for higher acuity patients (CTAS 1 and 2) because they are usually prioritized for physicians to see them quickly. The QI statistical process control run chart will be used to detect trends or patterns over the study time to demonstrate sustained change. SAS 9.2 (SAS Institute Inc) will be used for all analyses.

Results

The project was funded in June 2019 and approved by the research ethics board in February 2020. As of August 2021, for the retrospective SOC group, 3900 patients had been screened and 344 patients had been enrolled. There are currently 90 patients who have received the medical directive since its implementation in June 2020. The final study endpoint will be in June 2022. Interim results on reduction of time to diagnostic and therapeutic ED flow parameters and patient satisfaction are expected to be published in February 2022.

Discussion

Projected Significance

The projected significance of this study is to improve clinical outcomes for pediatric patients, empower nurses, increase patient and family satisfaction, reduce ED overcrowding, and improve ED flow metrics. ED wait times in Canada have been shown to lead to increased mortality and morbidity [23]; yet, there has been limited action to develop sustainable strategies to address this. COVID-19 caused a significant upheaval in ED capacity and volumes [24], and as the looming threat of variants continues, it is important to ensure that patients, especially those presenting with potentially emergent conditions, are seen more efficiently. Our study provides a novel method of addressing these concerns in a framework that can be applied to many other emergent clinical diagnostic pathways beyond appendicitis (eg, testicular torsion) and in both academic and community hospital sites.

Limitations

We aim to address several limitations in this study. First, this directive is heavily reliant on patient volumes, physician/nursing staffing, and time of patient arrival to the ED, as these directly affect ED flow metrics. To address this, an ED run chart will be constructed to visualize the impact the directive has had on primary outcomes and will be adjusted for these variables. To do this, we will record ED flow metrics for both patients who did and did not receive the directive throughout the study period. Second, it is necessary that this directive improves clinical outcomes without increasing resource use. This is especially important in ensuring that the results are better not simply because more imaging and blood work is being ordered but because they are being done for appropriate patient indications/presentations. This potential limitation will be addressed by analyzing the difference of proportion of patients who had a surgical appendectomy that were investigated using the nursing directive versus those that were physician initiated. Finally, although the directive may improve time to initial diagnostic imaging or to disposition (consult or discharge), it may not influence the speed at which teams such as radiology or pediatric surgery can perform imaging, assess the patient, and perform an appendectomy. Given the interprofessional nature of the project, the goal will be to iterate and gain feedback from other departments on how best to reduce these potential bottlenecks in our interim analysis and initial pilot results. In terms of patient/caretaker satisfaction, many factors affect a patient's experience beyond the ED, which may bias these results. As caretakers and patients can find it difficult to delineate the care in the ED from the ED staff versus surgery, pediatrics, or other providers once transferred, it will be

important to keep this in mind when evaluating qualitative feedback.

Comparison With Prior Work

Two prior studies [18,19] with similar concepts served as the basis for this integrative study. The authors involved with the studies have also served as collaborators for this study (GT, HF). The study done by Thompson et al [18], as previously mentioned, showed a significant time to reduction in time of triage to blood draw, hospital admission, and appendectomy. Our study adds additional outcomes such as patient satisfaction and time to US to further understand the effectiveness of this directive in quality of care and diagnostic efficiency. Another study [19] that was conducted at our institution examined the implementation of a standardized appendicitis care pathway for ED physicians. This study found that this process could reduce negative appendectomies, unnecessary computed tomography scans, and unnecessary hospital admissions. Our study built on this research and implemented this into the directive pathway, especially as it pertains to US imaging; however, we focused on nursing staff instead of physicians, as they are the first to see the patient prior to initial assessment by the physician.

Conclusions

Pediatric appendicitis is a common surgical emergency that can be diagnosed and treated more efficiently using an evidence-based advanced nursing medical directive. This initiative can improve patients' therapeutic outcomes, quicken diagnostic outcomes, empower nurses to begin the diagnostic workup, and improve patient and caretaker satisfaction with treatment provided in the ED. Our future goals are to publish the results of this initial pilot study and begin working with collaborators to implement this initiative into other institutions.

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Authors' Contributions

HC trained research assistants on the team, performed screening and enrollment of patients, worked with ME on protocol refinements, and led the manuscript creation and submission. MS performed screening and enrollment of patients and assisted in manuscript creation. RR and ER performed screening and enrollment of patients. ME is the principal investigator on the study and led all aspects of the study alongside conceptualizing and implementing the original protocol, the directive, and oversight of manuscript creation and submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient and caretaker satisfaction survey completed after the initial directive encounter.
[DOCX File , 192 KB - resprot_v10i10e33158_app1.docx]

Multimedia Appendix 2
Patient and caretaker satisfaction survey completed 7 days after the initial directive encounter.
[DOCX File , 26 KB - resprot_v10i10e33158_app2.docx]

Multimedia Appendix 3
Case report form for data capture on standard of care and directive patients.
[DOCX File , 63 KB - resprot_v10i10e33158_app3.docx]

Multimedia Appendix 4
Funded peer review letter.
[PDF File (Adobe PDF File), 672 KB - resprot_v10i10e33158_app4.pdf]

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Abbreviations

AND: advanced nursing directive
CTAS: Canadian Triage and Acuity Scale
ED: emergency department
IV: intravenous
LOS: length of stay
PAS: pediatric appendicitis score
QI: quality improvement
REDCap: Research Electronic Data Capture
RLQ: right lower quadrant
SOC: standard of care

US: ultrasound

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Protocol

An Intervention With Michigan-Grown Wheat in Healthy Adult Humans to Determine Effect on Gut Microbiota: Protocol for a Crossover Trial

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Abstract

Background: Daily fiber intake can increase the diversity of the human gut microbiota as well as the abundance of beneficial microbes and their metabolites. Whole-grain wheat is high in fiber.

Objective: This manuscript presents a study protocol designed to understand the effects of different types of wheat on gastrointestinal tract microbes.

Methods: Human adults will consume crackers made from three types of wheat flour (refined soft white wheat, whole-grain soft white wheat, and whole-grain soft red wheat). In this study, participants will alternate between crackers made from refined soft white wheat flour to those made from whole-grain soft white wheat and whole-grain soft red wheat flour. Survey and stool sample collection will occur after 7-day treatment periods. We will assess how wheat consumption affects gastrointestinal bacteria by sequencing the V4 region of 16S rRNA gene amplicons and the inflammatory state of participants' intestines using enzyme-linked immunosorbent assays. The butyrate production capacity of the gut microbiota will be determined by targeted quantitative real-time polymerase chain reaction.

Results: We will report the treatment effects on alpha and beta diversity of the microbiota and taxa-specific differences. Microbiota results will be analyzed using the vegan package in R. Butyrate production capacity and biomarkers of intestinal inflammation will be analyzed using parametric statistical methods such as analysis of variance or linear regression. We expect whole wheat intake to increase butyrate production capacity, bacterial alpha diversity, and abundance of bacterial taxa responsive to phenolic compounds. Soft red wheat is also expected to decrease the concentration of inflammatory biomarkers in the stool of participants.

Conclusions: This protocol describes the methods to be used in a study on the impact of wheat types on the human gastrointestinal microbiota and biomarkers of intestinal inflammation. The analysis of intestinal responses to the consumption of two types of whole wheat will expand our understanding of how specific foods affect health-associated outcomes.

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KEYWORDS

fiber; microbiota; whole grain; wheat; butyrate; calprotectin; lipocalin-2

Introduction

Background

An individual's gut microbial community is colonized by trillions of microorganisms [1]. These microorganisms interact with other cells, influencing important metabolic and immune functions. In this way, the gut microbiota can benefit the host, offering protection from pathogens and supporting immune regulation [2]. However, a dysbiotic gut microbiota is linked to disturbances in metabolic and biological processes, leading to a variety of chronic diseases as well as cancers [3]. Individuals with reduced bacterial richness are characterized by phenotypes such as increased adiposity and insulin resistance [3].

Dietary intake is strongly associated with the composition of the gut microbiota [4-9]. This effect of diet on the gut bacterial community can occur within days, quickly switching among functional profiles characteristic of different diets, and thereby making food intake an important factor for managing the gut microbiota [5,10]. The Western diet is characterized by foods low in fiber and high in fat and refined sugars and carbohydrates [11]. The Western dietary pattern results in a gut microbiota characterized by decreased bacterial diversity with specific losses of important microbes such as *Bifidobacterium* spp., *Lactobacillus* spp., and Bacteroidetes [12-15].

As ultraprocessed foods have become a common component of the Western diet, resulting in a loss of whole grains and fiber, the gut microbial composition has become enriched with proinflammatory microbes that correlate with metabolic risk factors and which contribute to noncommunicable chronic diseases such as obesity and type 2 diabetes [14,16,17]. Consumption of whole grains, especially when used as a replacement for refined grains, improves the gut microbiota and is inversely associated with diseases characterized by a gastrointestinal microbial community in dysbiosis [18]. Whole grains have a prebiotic effect on the gut and restore diversity [12]. Prebiotics are compounds known to support the growth of beneficial intestinal microbes [19]. Bifidobacteria and lactobacilli respond positively to increased consumption of whole grains, as observed in a diet intervention study by Costabile et al [12]. Therefore, whole grain consumption may counteract the inhibitory effects of the modern Western diet on these bacterial genera [12,20] and, thus, may be one method to restore gastrointestinal microbiota diversity.

Grains are a staple of the Western diet; however, grains exist in many forms. Thus, it is important to consider the types of grains being consumed [21,22]. The 2015 and 2020 United States Department of Agriculture dietary guidelines for Americans recommended that half of all grains come from whole grains; nevertheless, refined grains are a trademark of the typical Western diet [14,23]. Compared with the consumption of whole grains, consumption of refined grains is associated with a higher risk of chronic disease. In rodent models where the animals are inoculated with human microbiota, low dietary intake of microbiota-accessible carbohydrates for several generations caused reduced microbial diversity [7].

Similarly, in humans, differences in the gut microbiota have been observed among different geographic groups consuming their culturally habitual diets [7,24]. Thus, over subsequent generations, refined grain intake can compound lost intestinal diversity and obliterate some taxa, most specifically Bacteroidales and Clostridiales [7]. Furthermore, the addition of microbiota-accessible carbohydrates to the murine diet suppressed a clinically important intestinal pathogen, *Clostridium difficile* [25]. Recent research has focused on replacing processed foods with whole foods to prevent this loss in microbial diversity and support gastrointestinal health [12,13].

Whole grains are rich in carbohydrates accessible to the gut microbiota, which bacteria can use for food and energy [26]. Consequently, adding whole grains to the diet leads to increased gut fermentation [15]. This process produces short-chain fatty acids, notably butyrate, an important anti-inflammatory and antioxidant molecule [15]. Diets rich in fiber have been positively associated with the presence of bifidobacteria and other lactic acid–producing bacteria and are associated with a shift toward long-term maintenance of metabolic and immune health [15]. Whole-grain wheat is a good source of fiber. Thus, increasing whole-grain wheat intake increases fiber intake, leading to a more diverse microbiome that not only contains the beneficial microbes themselves but also contains their metabolites [27].

Additional components of whole-grain wheat that convey health benefits are polyphenols [28]. Polyphenols act as antioxidants and prebiotics in the gut and, as such, interact with the gut microbial community affecting its composition [29]. When compared with the consumption of refined wheat, consumption of whole wheat increases the absorption of phytochemicals and the subsequent excretion of fecal ferulic acid, a polyphenol metabolite [13,30]. An increase in the availability of fecal ferulic acid through the feeding of whole grains has been associated with a significant increase in *Bacteroidetes* in the gut [13,20]. Thus, the positive relationship between whole grain ferulic acid and certain taxa of the gut microbiota is proposed as a possible mechanism for the alleviation of gut inflammation [13]. As different types of wheat have different polyphenolic content, it is important to understand how they differ in their relationship with the gut microbiota.

Objectives

To fully understand the impact of whole-wheat products on humans, we must understand the effects of different types of wheat (ie, white vs red or hard vs soft) on human gastrointestinal tract microbes. However, previous studies have ignored these differences in wheat types. Therefore, we describe a protocol in which we will feed human adults crackers made from three different types of wheat flours and assess how cracker consumption affects (1) the gastrointestinal microbial communities and (2) the inflammatory state of the intestines. We hypothesize that whole-grain soft white wheat flour will promote different microbes compared with whole-grain soft red wheat flour. In addition, we expect that the whole-grain soft red wheat treatment will result in decreased intestinal inflammation compared with the refined white wheat flour treatment. The successful completion of the proposed research will improve

our understanding of the unique effects of different types of wheat on the human gut microbiota and the inflammatory state of the gastrointestinal tract.

Methods

Design

This wheat intervention study will characterize the variable response of gut bacteria to supplementation in adult humans. Treatments will include (1) refined soft white wheat flour, (2) bran-containing whole-wheat flour of Michigan soft white wheat, or (3) bran-containing whole-wheat flour of Michigan soft red wheat. All 3 flour samples will be provided by King Milling Company (Lowell, Michigan). Each of the two whole-wheat interventions will be administered over a 1-week period, with a baseline week (refined soft white wheat flour) before the intervention begins and a washout week (refined soft white wheat flour) between the two test periods (Figure 1). Wheat flour will be administered to participants in the form of wheat crackers. The nutrient composition of the wheat crackers is provided (Table 1)**.** During each of the two test periods, 80 g of crackers made from whole-grain soft white wheat flour or whole-grain soft red wheat flour will provide each participant with approximately 10.7 g of total dietary fiber per day (Table 1). At the end of each 1-week treatment period, a stool sample as well as answers to a health and fiber intake questionnaire, will be collected from each participant. A total of 4 stool samples will be collected from each participant over the course of the study. Microbiome samples will be aliquoted and stored at −80°C until analysis.

Figure 1. Overview of study design. ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction.

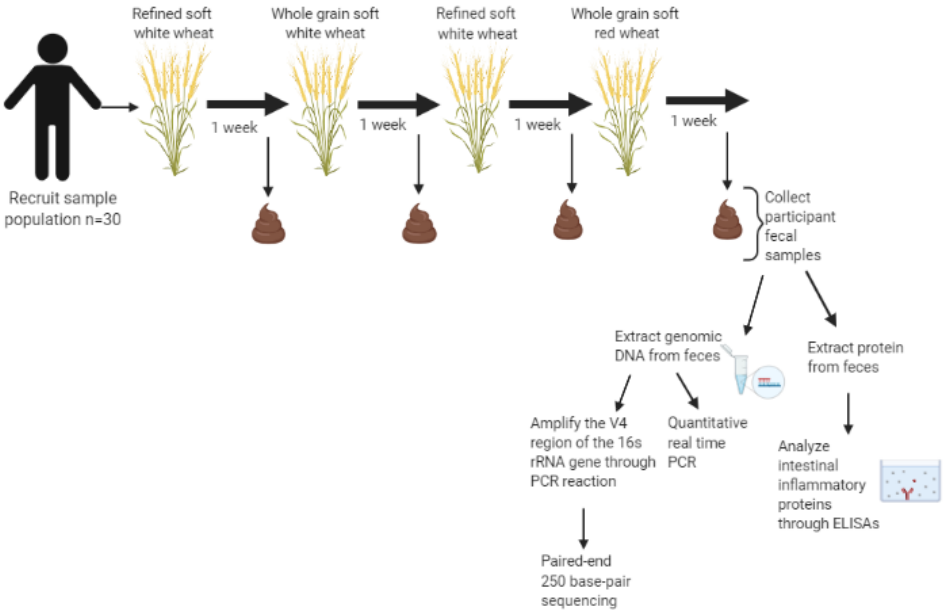

Table 1. Nutrient composition of test crackers.

Nutrient composition	80-g portion of crackers		
	Refined soft white wheat flour crackers	Whole-grain soft white wheat flour crackers	Whole-grain soft red wheat flour crackers
Calories (kcal)	313	298	306
Fat (g)	6.44	7.16	8.00
Saturated fat	1.68	1.82	2.08
MUFA[a]	1.26	1.41	1.59
PUFA[b]	3.16	3.54	3.92
Trans fat	0.058	0.071	0.082
Protein (g)	7.15	9.10	9.35
Carbohydrates (g)			
Total dietary fiber	3.99	10.72	10.72
Insoluble fiber	1.54	7.54	7.35
Soluble fiber	2.45	3.18	3.37
Sodium (mg)	439	452	454

[a]MUFA: monounsaturated fatty acids.

[b]PUFA: polyunsaturated fatty acids.

Setting and Participant Recruitment

This study will be conducted during the summer in East Lansing, Michigan, on the campus of Michigan State University and will enroll 30 adults. Subjects will be recruited via flyers hung in buildings around the Michigan State University campus as well as through the Michigan State University–paid research pool [31]. To be included in the study, participants must be aged between 18 and 55 years as the gut microbiota matures by adulthood and remains stable throughout [1]. Participants must also have bowel movements at least once every 3 days, be willing to eat wheat crackers, and be available for weekly lab visits. Participants will be excluded if they take any nonsteroidal anti-inflammatory drugs, antacids, proton pump inhibitors, nutritional supplements, or multivitamins daily; have taken any antibiotics in the 2 weeks before the study; have gastrointestinal issues or diabetes; are pregnant; are following any special diet; or have food allergies. Participants will be provided with a US $50 cash incentive upon completion of the dietary intervention. All participants will provide written informed consent.

Dietary Intervention

The dietary intervention will consist of a 4-week period of wheat consumption in the form of wheat crackers. Each week, participants will be given 7 bags of crackers (1 bag for each day of the week), containing approximately 80 g of baked crackers per bag, to be eaten throughout the following week. Each 80 g cracker allotment will provide approximately 10.7 g of total dietary fiber for crackers made from either whole-grain soft white flour or whole-grain soft red flour. The nutrients and calories of the 80 g cracker allotment consumed per day are listed in Table 1.

Crackers for each treatment week will be made in bulk to yield 260 daily portions (7 portions per participant plus extra), with approximately 80 g of baked crackers per daily portion per person. The cracker was formulated as 100 g flour (approximately 13% moisture), 1.5 g of iodized salt, 2 g of sugar, 6 g of vegetable shortening, and 49 to 50 g of tap water. The proportions of flour, salt, and sugar, according to the formulation stated above, will be added into the bowl of a Hobart mixer (model A-200) and whisked to combine the dry ingredients. Fat will be added to the dry ingredients and mixed until the fat particles are reduced in size to approximately 1 to 2 mm. Water will then be added and mixed until a firm dough forms. The amount of water (approximately 48 g) will need to be adjusted to ensure that all flour is fully hydrated. The dough will then be portioned by dividing it into 127 g aliquots based on the expected yield of 80 g of baked crackers per 127 g of dough (determined in preliminary testing). Each 127 g portion will be flattened between two pieces of parchment paper using a dough sheeter set to 3/32 inch. The top sheet of the parchment paper will be removed, and the dough will be cut into approximately 1- to 2-cm-wide strips. Crackers from each portion of dough will be baked in a carousel oven for approximately 11 to 12 minutes at 400 °F until browned. Crackers will be cooled on a rack on the workbench before being placed into individual resealable portion bags labeled *day 1* to *day 7*; then, 7 bags will be placed in one larger bag to be distributed to each participant.

As this study involves adding approximately 300 calories of carbohydrate-containing food to the daily diet, participants will receive flyers (Figure 2) informing them how to incorporate the crackers into their diets by replacing everyday dietary items such as cereals and bread with the test crackers. This will prevent or minimize participants' weight gain.

Figure 2. Flyer to be distributed to participants providing calories in common serving sizes of typical carbohydrate-containing foods.

Outcomes

Overview

At the conclusion of each week, stool samples will be collected for analysis. The primary outcome measure will be the alpha diversity of the gut microbiota. This will be measured using the sequencing data obtained from the participants' stool samples after DNA extraction and polymerase chain reaction (PCR) amplification of the V4 region of the 16S rRNA gene. The secondary outcome measure will be biomarkers of gastrointestinal inflammation, as measured by protein concentrations of calprotectin and lipocalin-2 in protein extracts of the stool samples. Furthermore, the microbiota beta diversity, abundance of *Bifidobacterium* and *Lactobacillus*, and butyrate production capacity of the gut microbiota will be assessed after each week of treatment. The abundance of *Bifidobacterium* and *Lactobacillus* will be determined from the sequencing results. The butyrate production capacity will be determined by

quantitative real-time PCR assays targeting the bacterial butyrate kinase and butyrate transferase genes [32].

Other Measurements

Background characteristics of the study participants will be recorded during recruitment when each participant will complete a short questionnaire. In addition, current weight, health status, 24-hour dietary intake, and water source will be collected each week along with a fiber intake questionnaire (described below) recording the amount of fiber-containing foods consumed throughout the week. A 24-hour recall will be implemented as this has been previously reported to supply sufficient information to interpret microbiota data from participants' fecal samples [33]. Participants will self-report their 24-hour dietary intake by free response to the question "What did you eat and drink in the past day? (Please give as much detail as possible, including the estimated amounts)."

Data Analysis

Diet Analyses

Overview

Individual diet diversity scores will be calculated for each participant at each time point. The use of the diet diversity score provides a more general measure of the variety of dietary intake than specific food consumption data. This scoring system counts the number of food groups consumed by an individual. Data will be supplied based on the 24-hour intake data provided in response to this prompt, "What did you eat and drink in the past day? (Please give as much detail as possible, including the estimated amounts.)" as well as their answers to a checklist of 34 food and supplement items where participants are prompted to "Place an 'x' in the box next to anything that you ate in the past 24 hours." The food checklist was designed to capture the intake of the foods listed in the diet diversity scoring tool document of the Food and Agriculture Organization of the United Nations [34]. Dietary diversity score will be assessed as described by the Food and Agriculture Organization of the United Nations [34].

Fiber Intake Analysis

The PhenX fiber intake protocol will be used to assess additional dietary fiber intake [35]. Each week, participants will receive a screener (PhenX protocol 50601) asking them to report how often they consumed different types of fiber-containing foods (ie, cereal, vegetables, and beans). Participants will record how often they consumed a portion of food—never, less than once a day, once a day, twice a day, three times a day, four times a day, or five or more times per day. A score will be assigned to each participant at each time point using the scoring methods provided by the PhenX protocol. This score will be used to account for the fiber in the diet that is not from the test crackers.

Microbiota Analyses

Stool samples will be extracted, prepared for sequencing of the 16S rRNA gene, and sequenced as described in references [36-38].

Butyrate Gene Analyses

Quantitative real-time PCR will be performed on the genomic DNA from each sample to determine the levels of butyryl-CoA: acetate CoA-transferase (*but*) and butyrate kinase (*buk*). Primer sets, But_RosEub, But_G.prausn, and Buk, previously designed by Vital et al [32], will be used. All genomic DNA samples will be diluted to 2.5 to 5 ng/µL. In a 96-well plate, genomic standards at concentrations of 10^2 to 10^7 will be used to create a standard curve. All wells will be filled with 7.5 µL SYBR Green, 3.5 µL ddH_2O, 1 µL F primer, 1 µL R Primer, and 2 µL template. The thermocycling program to be performed is as follows: 2 minutes at 50°C, 10 minutes at 95°C, 45 seconds at 95°C, 45 seconds at annealing temperature for the specific primer, and 45 seconds at 72°C for 40 cycles. A one-way repeated-measures analysis of variance (ANOVA) will be performed on each set of data to compare the relative abundance and presence of the following butyrate synthesizers: *Faecalibacterium prausnitzii*, *Eubacteria* spp., *Roseburia* spp., and *Clostridium acetobutylicum*.

Intestinal Inflammatory Protein Analyses

Proteins will be extracted from the stool samples. The extraction buffers for lipocalin (catalog number 30757) and calprotectin (catalog number 30473) will be purchased from Epitope Diagnostics, Inc. First, the fecal samples will be aliquoted and stored at −80°C until protein extractions are performed. Then, approximately 100 mg of fecal material will be aliquoted into a conical tube, and the exact weight of the sample will be recorded. Each sample will be extracted separately with each of the two extraction buffers. Using a serological pipette, 4 mL of extraction buffer per 100 mg of stool will be aliquoted into a conical tube for each sample. Each tube will be gently vortexed and incubated at room temperature on an orbital shaker for 30 minutes. The protein extracts will then be aliquoted into microfuge tubes and stored at −80°C until ELISAs (enzyme-linked immunosorbent assays) are performed. The ELISA kits will be purchased from R&D Systems (a Bio-Techne brand) for human calprotectin (S100A8/S100A9; DS8900) and human lipocalin-2 (neutrophil gelatinase-associated lipocalin; DLCN20). Fecal extracts will be diluted at 1:25 or 1:100 in sample diluent for calprotectin assays and 1:20 or 1:100 in sample diluent for neutrophil gelatinase-associated lipocalin assays.

Statistical Analyses

Statistical analysis of differences between pre- and posttests will be assessed using ANOVA or Friedman Wilcoxon rank-sum tests [39]. Multivariate statistics will be performed using R (R Foundation for Statistical Computing), a free statistical software program. To compare the alpha diversity of the microbial communities, Chao1 (a measure of richness), inverse Simpson (a measure of richness and evenness, with emphasis on evenness), and Shannon diversity (a measure of richness and evenness, with emphasis on richness) will be calculated in R using the vegan package [40]. ANOVA and Wilcoxon signed-rank test or Friedman test with post hoc comparisons will be used to compare alpha diversity across treatment categories after intervention [41]. For beta diversity, Bray-Curtis and Sorenson distances will be used with principal coordinates

analysis ordination to produce plots of the distances between samples. Differences in beta diversity between time points will be determined using permutational multivariate ANOVA (PERMANOVA) via the adonis function in the vegan package, and differences in group dispersion will be determined using PERMDISP [40]. PERMANOVA may also be used to determine the relationship between the distance metrics and wheat variety, as well as other variables. Metastats (a function of the mothur software package) will be performed on the subsampled abundance data to test for significant differences in operational taxonomic unit abundance between groups [42]. Changes in taxa (both genus and phylum level) >1% average relative abundance will be determined across time points using the Friedman test with post hoc comparisons. Where appropriate, the negative binomial and zero-inflated mixed models in the R package will be used to test for differences in taxa abundance over time [43].

Enterotypes will be manually assigned based on clustering within quadrants in a Bray-Curtis principal coordinates analysis plot overlaid with the most abundant taxa driving community differences, as in Wu et al [4], using the envfit function in the vegan package. Significant differences between enterotypes will be determined using ANOVA for parametric data and the Kruskal-Wallis test for nonparametric data. Differences between time points within each enterotype will be determined using the Friedman test with post hoc comparisons.

Response Analysis

If only a subset of participants is found to respond to the treatment, response groups will be determined by an individual's change in alpha diversity metrics across the treatments. A participant will be considered a *positive responder* if alpha diversity (either Chao1, Shannon, or inverse Simpson) is greater at time points B and D (whole wheat) than at both A and C (refined white wheat). However, if this change is not observed, participants will be considered *nonresponders*. After post hoc assignment of response groups, differences in overall alpha diversity between positive responder and nonresponder groups will be tested with ANOVA (if parametric) or Wilcoxon ranked-sum (if nonparametric). The normality of data will be determined using the Shapiro-Wilk test. Differences will be tested within each time point. Beta diversity differences between response groups will be determined at each time point using PERMANOVA and PERMDISP. Continuous demographic variables (age, BMI, and fiber intake) will be compared with a two-tailed *t* test if parametric and a Wilcoxon rank-sum test if nonparametric, with normality confirmed using the Shapiro-Wilk test. The Fisher exact test will be used to determine the independence of sex, smoking exposure, and race regarding response to treatment. Differences in genera present at >1% average relative abundance will be tested between response groups using a negative binomial model in the MASS package [44].

Results

The study procedures were approved by the Michigan State University institutional review board (IRB #00002638) in spring 2019. Sample collection occurred in summer 2019. The results of this research are expected to be published in late 2021.

Discussion

Impact

The primary aim of this study is to measure the alpha diversity of gut microbiota following each week of cracker treatment to determine whether whole-wheat consumption increases alpha diversity. Additional aims are to measure the levels of gastrointestinal inflammation as well as *Bifidobacterium*, *Lactobacillus*, and butyrate-producing bacteria that are present following each treatment. These analyses will elucidate how different types of wheat may affect the gastrointestinal tract microbiota.

Only recently have we begun to understand the mechanism by which whole grains promote health [12,16,21,45]. Various microbes and metabolites have been hypothesized to decrease inflammation; however, much is still unknown [14]. Our aim—to measure how microbial diversity and levels of certain bacteria are affected by whole-wheat intake—will elucidate the potential mechanisms by which whole grains affect health. In addition, little is known about the effects of different types of wheat (eg, white vs red) on the gut microbiota. Specific wheat types have different molecular compositions and may therefore promote different microbes [46-49]. Taking into account the effects of different types of whole wheat will allow us to understand better the food characteristics that underlie the impact of whole-wheat consumption on humans.

We anticipate that the results of this intervention study will have implications for both wheat producers and consumers. Recent trends suggest an increase in the number of consumers who avoid wheat products as part of new diets that emphasize carbohydrate reduction, despite the unclear benefits of avoidance in those without celiac disease [50]. In fact, the risks of avoiding gluten, and subsequently whole grains, include deficiency of micronutrients, fiber, and an increased consumption of refined products, which may outweigh the perceived benefits of avoiding wheat [50]. Understanding how microbes and gastrointestinal inflammation are affected by the consumption of whole-grain wheat may increase the consumption of whole-grain wheat by health-conscious consumers.

Strengths and Weaknesses

An important strength of this study is the composition of the crackers. The aim of the study is to test the effect of specific types of wheat; thus, it is important to note that we have created a cracker formulation that is composed almost entirely of the wheat of interest with few additional ingredients. The simple recipe we have developed for the crackers will improve confidence that the differences observed in the microbial community and inflammatory biomarkers are owing to the consumption of the wheat in the study crackers rather than a different ingredient in the treatment food. The quick turnaround from the cracker intake to sample collection also helps strengthen the study. Stool samples will be collected on the final day of each week's cracker intake, ensuring that little time has elapsed between the last cracker intake and stool sample

collection. This is important for microbiota analyses as the temporal intake of food is tightly associated with microbial composition [51]. In addition, we will allow sufficient time to pass between each intervention through the use of a washout period. Johnson et al [33] described a minimum 3- to 5-day period between crossing-over diets to allow the microbiome to return to baseline. The crossover design of this study will allow us to perform within-person comparisons, placing less emphasis on interindividual differences in the gut microbiome [33].

A potential limitation of our study may be participant retention. Participants will be expected to consume approximately 80 g of crackers every day for 4 weeks, so it is important that they enjoy the taste of the crackers to ensure their compliance and continuance in the study. However, the study participants may tire of the taste of the crackers. A high dropout rate could hinder our ability to detect statistically significant differences.

Whole grains alleviate dysbiosis in the gut microbiota; however, little is known about the impact of different wheat types on this phenomenon [12,18,20]. A 4-week wheat intervention to investigate the effect of different types of Michigan-grown wheat on the gut microbiota is described in this protocol. The results of this study will improve our understanding of the unique effects of different types of wheat on gut microbiota and on the inflammatory state of the human gastrointestinal tract.

Acknowledgments

Figure 1 was created at BioRender. This study is funded by the Michigan Soft White Wheat Endowment and Michigan State University AgBioResearch.

Authors' Contributions

SSC, LSG, and PKWN designed the study and critically revised the manuscript. SSC and PKWN wrote the proposal for the funding agency. GAK wrote the manuscript. ENH outlined the statistical analysis plan. All the authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
ELISA: enzyme-linked immunosorbent assay
PCR: polymerase chain reaction
PERMANOVA: permutational multivariate analysis of variance

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Protocol

The COVID-19 Study of Healthcare and Support Personnel (CHAMPS): Protocol for a Longitudinal Observational Study

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Abstract

Background: Early in the development of the COVID-19 pandemic, it was evident that health care workers, first responders, and other essential workers would face significant stress and workplace demands related to equipment shortages and rapidly growing infections in the general population. Although the effects of other sources of stress on health have been documented, the effects of these unique conditions of the COVID-19 pandemic on the long-term health and well-being of the health care workforce are not known.

Objective: The COVID-19 Study of Healthcare and Support Personnel (CHAMPS) was designed to document early and longitudinal effects of the pandemic on the mental and physical health of essential workers engaged in health care. We will investigate mediators and moderators of these effects and evaluate the influence of exposure to stress, including morbidity and mortality, over time. We will also examine the effect of protective factors and resilience on health outcomes.

Methods: The study cohort is a convenience sample recruited nationally through communities, professional organizations, networks, social media, and snowball sampling. Recruitment took place for 13 months to obtain an estimated sample of 2762 adults who provided self-reported information administered on the web through structured questionnaires about their work environment, mental and physical health, and psychosocial factors. Follow-up questionnaires will be administered after 6 months and annually thereafter to ascertain changes in health, well-being, and lifestyle. Participants who consented to be recontacted form the longitudinal cohort and the CHAMPS Registry may be contacted to ascertain their interest in ancillary studies for which they may be eligible.

Results: The study was approved by the Institutional Review Board and launched in May 2020, with grants from Travere Therapeutics Inc, McKesson Corporation, anonymous donors, and internal funding from the M. Louise Fitzpatrick College of Nursing at Villanova University. Recruitment ended in June 2021 after enrolling 2762 participants, 1534 of whom agreed to participate in the longitudinal study and the registry as well as to be contacted about eligibility for future studies.

Conclusions: The CHAMPS Study and Registry will enable the acquisition of detailed data on the effects of extended psychosocial and workplace stress on morbidity and mortality and serve as a platform for ancillary studies related to the COVID-19 pandemic.

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KEYWORDS

COVID-19; SARS-CoV-2; stress; depression; anxiety; sleep; social support; resilience; mental health; physical health

Introduction

Background

Globally, SARS-CoV-2 has infected more than 224 million individuals, with more than 41 million cases in the United States [1]. The first report that a new coronavirus was the cause of a spate of pneumonia cases in Wuhan, China, was issued in early January 2020 by the World Health Organization, and the first case in the United States was reported two weeks later [2]. By early spring of 2020, infections had risen dramatically in several countries, and projections suggested that the pandemic could impose severe strains on the ability of US hospitals to deliver care [3]. Experience from the severe acute respiratory syndrome (SARS) outbreak in 2003 [4,5] suggested that because of its heavy burden on the health care system, the rapidly rising number of COVID-19 cases would have a large impact on the mental and physical health of the health care workforce. Such concerns indeed began to emerge early in the spring of 2020 [6]. It also seemed reasonable to expect that laboratory workers, office personnel, first responders, and others who were engaged less directly in caring for patients with COVID-19 as compared to health care workers, would experience similar strains on their psychological well-being. First responders, including police, fire, and emergency medical services, may experience higher rates of exposure to SARS-CoV-2 than the general population [7].

Health care systems in numerous countries were overwhelmed by the COVID-19 pandemic, which has caused increased pressure on frontline health workers [8]. Hospitals in New York City**,** for example, have had to reconfigure patient-care spaces and restructure clinical teams rapidly to address the increase in the number of patients with COVID-19 [9]. The overwhelming workload, increasing numbers of suspected and confirmed COVID-19 cases, lack of evidence-based treatments, shortages of personal protective equipment (PPE), extensive media coverage, and perceptions of inadequate support may contribute to the mental burden of health care workers [10].

Concerns of health care workers that they might not only become infected with COVID-19 but also transmit it to family members and friends add to their psychological burden [9]. The combined result is that the COVID-19 pandemic can be expected to have a prolonged impact on the mental health of a broad range of workers who are essential for delivering health care [11,12].

Rationale

In the context of the COVID-19 pandemic, we anticipated that health care workers would face anxiety and depressive symptoms due to traumatic patient-care experiences and the risk of SARS-CoV-2 infection to family, friends, and colleagues [13]. Frontline health care workers were among the most vulnerable groups at risk of mental health issues during the early phases of the COVID-19 pandemic; however, the numerous risks to the well-being of health care workers remain poorly understood [14]. High prevalence of anxiety and depressive symptoms among frontline health care workers caring for patients with COVID-19 has been reported [14], but their duration and impact on future physical health are not known. The risks to the mental well-being of health care workers are likely multifaceted, with a dearth of information regarding who might benefit from preventive interventions [15].

Even under normal circumstances, workplace stress has effects on physical health [16], and these effects increase as decision latitude and control over work decrease [17]. With rapidly increasing caseloads in health care facilities, the COVID-19 pandemic seemed ideally constituted to create a high-demand, low-decision latitude environment. Added to this was the likelihood of a high proportion of adverse outcomes and mortality of patients due to the absence of effective treatments in the first months of the pandemic. Finally, PPE shortages [9,14,18] increased the risk of infection for health care workers and those with whom they have a close relationship, including family, household members, and others, which has the potential to add to other sources of stress.

Emotional stress and stressful life events have been shown to contribute to the six leading causes of death in the United States—cancer, coronary artery disease, accidents (unintentional injuries), respiratory disorders, cirrhosis of the liver, and suicide—as well as to type 2 diabetes, sleep disorders, and other health conditions [19]. Workplace stress in particular has been associated with hypertension [20] and coronary heart disease [21]. High workplace demands and low decision latitude, combined with low rewards, are prospective risk factors for common mental disorders [22]. The effects of stressful working conditions on the short-term mental health of health care personnel during this pandemic have already begun to emerge [9,18].

The effects of stress on long-term physical and mental health can take many years to become manifest. Military combat deployment [23,24] and elevated symptoms of posttraumatic stress disorder (PTSD) in civilians have been associated with increased risk of hypertension, myocardial infarction, and stroke [25,26]. Longitudinal trends show that the likelihood of developing multiple physical symptoms over time is higher for those who were deployed in combat than those without combat experience [27].

Research on the effects of stress on the COVID-19 workforce [9,18] is underway but is in its early stages [28], with mixed results [29]. Some studies have noted the potential importance of resilience in response to stress, including in health care workers [30], but adequate supporting data on the role of resilience in response to stress are lacking [31]. The COVID-19 pandemic experience of essential workers provides an opportunity to develop new information on the influence of sustained stress on the short- and long-term physical and mental

health of the workforce involved in providing health care or to support health care personnel, as well as on the potential influence of aspects of resilience and its role in moderating the effects of stress.

Based on the extensive body of literature on the psychosocial influences on health, it is likely that the COVID-19 pandemic will have deleterious effects on the health of health care workers and support staff in a broad range of professions [32]. Over time, as COVID-19 treatments and management improve and infection rates decrease through public health measures and vaccination, we anticipate that sources of stress will decrease, resulting in a gradient of influence on health among health care workers who enroll in the COVID-19 Study of Healthcare and Support Personnel **(**CHAMPS) during later phases of the pandemic. The CHAMPS Study and Registry is designed to ascertain the time course and magnitude of these changes on the long-term mental and physical health of essential workers in the health care environment.

Objectives

The objective of the CHAMPS Study and Registry is to assess the short- and long-term physical, social, and behavioral health of personnel ("essential workers") involved in supporting or delivering care for patients with COVID-19. Included are first responders, maintenance and support staff working in clinical settings, and health care professionals of all specialties and services. At enrollment, baseline data were obtained on the study participants' working environment, lifestyle, and mental and physical health. Subsequent waves of data collection will obtain follow-up information after 6 months and then annually through 2024. The study was approved by the Villanova University Institutional Review Board (IRB) in May 2020.

The primary objectives of the CHAMPS study are to (1) determine the extent to which working in health care affects future physical and mental health; (2) evaluate trends over the time course of the evolving pandemic; (3) identify exposure variables that are associated with incident changes in health over time; and (4) identify factors that influence short- and long-term health. Specific hypotheses include the following:

1. Measures of mental health symptoms of anxiety, traumatic stress, depression, insomnia, disordered eating, resilience, burnout, and poor self-reported health will be more prevalent in essential workers than in the general population and greater in magnitude than reported in similar populations before the COVID-19 pandemic.
2. The severity of mental health symptoms will be associated with prevalence of SARS-CoV-2 infection rates in the geographic region in which the study participants work.
3. Mental health symptoms will persist longer among study participants with more severe symptoms.
4. Essential workers who report elevated symptoms of anxiety, traumatic stress, or depression will experience exacerbation of existing physical health conditions over time and higher incidence of new physical health conditions.
5. Severity and progression of mental and physical health conditions will be exacerbated by the degree of perceived exposure to adverse working environments, such as availability of personal protective equipment, extended working hours, and adequacy of staffing levels.

Methods

Study Components

CHAMPS consists of three components: (1) a cross-sectional study of respondents who consented to participate in a single assessment of health; (2) a longitudinal study of participants who consented to repeated waves of data collection; and (3) a registry comprised of participants who enrolled in the longitudinal study. The registry serves as a source of study participants who may be eligible for future ancillary observational studies as well as randomized clinical trials.

Questionnaires

To address the specific hypotheses, we selected validated instruments available for mental and physical health variables of interest. They are described in detail in the *Measures* section. Demographic, occupation, work environment, and geographic questions were written by professionals who work in health care.

Participants and Recruitment

Eligible participants were adult essential workers involved in health care. For the purposes of the CHAMPS study, essential workers were defined as adult (aged 18 years or older) health care personnel, support personnel, and first responders working in any health care facility or in the community. Included were those working in facilities that are involved in patient care, such as hospitals, clinics, private practices, or screening facilities; those directly involved in patient care (eg, physicians, nurses, phlebotomists, respiratory therapists, pharmacists); laboratory staff; service employees (office staff, maintenance, housekeeping, food service); individuals working in long-term care facilities; and first responders (eg, police officers, firefighters, emergency medical technicians, paramedics). Collectively, we refer to these as "essential workers." Enrollment took place over 13 months, from May 2020 through June 2021, throughout the United States.

Recruitment included advertising through local and national professional and trade organizations, news, social and professional media, alumni organizations, and word of mouth to describe the study and disseminate the internet link that provided access to the informed consent form and study questionnaires. Professional and trade organizations were identified and contacted. Website posts, e-newsletters, and social media were used to reach members of eligible occupations, with news or social media posts either by their group administrators or by the study team. The wider social media universe was reached through posts on university channels on various platforms, university-affiliated influencer posts, and a limited paid media campaign. Social media posts and outreach to organization leaders continued periodically throughout the recruitment period.

Informed Consent

An internet link provided access to the informed consent document that described the purpose of the study, time required

to complete the questionnaire, duration of the study, and options for cross-sectional or longitudinal study participation. An affirmative consent response opened the baseline questionnaire. At the end of the initial survey, participants were asked to provide their email contact information for the longitudinal study and registry, which would be used to provide them with future questionnaires and information about studies for which they might qualify. The consent form also stated that information would be used only for medical research and shared only with other medical researchers. Participants were informed that they could end participation at any time.

Registration

CHAMPS has been registered at ClinicalTrials.gov (NCT04370821).

Measures

The baseline questionnaire consisted of questions related to the participants' demographic information, occupation, and work environment, followed by validated instruments on behavioral health, described below. Instruments were selected to balance validity and brevity. An open-ended question provided an opportunity to describe personal experiences of working during the COVID-19 pandemic and participants' interest in being interviewed. The measures and timepoints of data collection are outlined in Table 1.

Table 1. COVID-19 Study of Healthcare and Support Personnel (CHAMPS) measures and data collection timepoints. All data are self-reported.

Measure	Instrument	Items, n	T0 (baseline)	T1 (6 months)	T2 (Year 1)	T3 (Year 2)	T4 (Year 3)	T5 (Year 4)
Demographics	N/A[a]	N/A	✓					
Anxiety	GAD-7[b]	7	✓		✓	✓	✓	✓
Depression	PHQ-2[c]	2	✓		✓	✓	✓	✓
Social support	OSSS-3[d]	3	✓					
Sleep	ISI-7[e]	7	✓		✓	✓	✓	✓
Traumatic stress	IES-R[f]	22	✓		✓	✓	✓	✓
Stress specific to COVID-19	Based on Wu et al [4] and Chong et al [5]	10	✓					
Resilience	BRS[g]	6		✓	✓	✓	✓	✓
Proactive Coping	Proactive Coping Subscale of the PCI[h]	14		✓				
Burnout	OLBI[i]	16		✓	✓	✓	✓	✓
Eating habits	LOCES[j]	7		✓	✓	✓	✓	✓
Morphometric	Height, weight	2		✓				
Alcohol and substance abuse	N/A	2		✓				
Physical activity	N/A	2		✓				
Health history checklist	N/A	14		✓	✓	✓	✓	✓

[a]N/A: not applicable.

[b]GAD-7: Generalized Anxiety Disorder-7.

[c]PHQ-2: Patient Health Questionnare-2.

[d]OSSS-3: Oslo Social Support Scale-3.

[e]ISI-7: Insomnia Severity Index-7.

[f]IES-R: Impact of Events Scale - Revised.

[g]BRS: Brief Resilience Scale.

[h]PCI: Proactive Coping Inventory.

[i]OLBI: Oldenburg Burnout Inventory.

[j]LOCES: Loss of Control Over Eating Scale.

Demographic Data, General Health Status, and SARS-CoV-2 Infection

These will be ascertained by specific questions related to age, sex, occupation, self-reported general health, and infection status at the time of enrollment.

Anxiety and Depression

Anxiety symptoms will be assessed by the Generalized Anxiety Disorder-7 (GAD-7) [33], and depressive symptoms will be assessed by the Patient Health Questionnaire-2 (PQH-2) [19]. The GAD-7 was validated on 2740 adults, of whom 965 were interviewed by a mental health professional. The PHQ-2 includes the first 2 items of the PHQ-9, whose sensitivity and specificity are associated with the prevalence of depression [34]. These instruments were selected for their performance and brevity.

Social Support

The Oslo Social Support Scale-3 (OSSS-3) [35] will be used to measure social support. We sought a brief social support scale with good psychometric properties. With a Cronbach α of .640, the 3-item OSSS has good internal consistency and acceptable construct validity [35], especially for a short scale. It is scored easily, with normative values available for men and women between the ages of 14 and 91. In a cohort of adults 50 to 69 years of age who experienced adverse childhood events, moderate to strong perceived social support scores as measured by the OSSS-3 were associated with significantly lower odds of depressive symptoms [36].

Sleep Quality

The Insomnia Severity Index-7 (ISI-7) will be used to measure sleep quality. The ISI-7 has been validated as a useful clinical tool to quantify perceived insomnia severity for primary as well as secondary insomnia and in young and older patients [37]. It has also been validated for web-based applications, as the psychometric properties of the web-based version were found to be similar to those of the form version [38]. In a study of medical staff in China following the COVID-19 outbreak, ISI-7 scores were associated with anxiety levels and isolation and moderated by level of education [39].

Stress

Stress has been associated with elevated risk of cardiovascular, metabolic, and musculoskeletal disorders [18]. Essential workers may experience stress from numerous sources that are not necessarily related to the pandemic. These may interact with stressors that are related to COVID-19 work life, suggesting that both general stress and stress specific to COVID-19 should be ascertained. We will measure *traumatic stress* with the Impact of Events Scale - Revised (IES-R) [40], which assesses the symptoms of PTSD. For *stress specific to COVID-19*, we adapted scales from Wu et al [4] and Chong et al [5] to assess the work environment and concerns specifically related to working in a high-risk environment.

Narrative Response Question

The last question on the questionnaire provides the participants with an opportunity to describe their service experiences during the pandemic in narrative form for qualitative analysis, with no limits on the time or length of the narrative.

Six-Month Follow-up

The first follow-up occurred 6 months after enrollment and completion of the baseline questionnaire. Assessments included resilience, burnout, eating habits, and alcohol and substance use; physical activity; nutrition; height, weight, and weight discrimination items [41,42]; and a comprehensive health history checklist.

Resilience

Resilience will be measured by the Brief Resilience Scale (BRS), which is designed to assess the ability to bounce back from stress and to be brief [43]. It includes 3 positively and 3 negatively worded items, which is thought to reduce the effects of social desirability and positive response bias. This scale is unique because it assesses resilience rather than the attributes that contribute to resilience. Whether any aspects of resilience in middle life predict long-term health outcomes after major life events such as the COVID-19 pandemic remains to be determined.

Proactive Coping

Proactive coping is defined as a forward-looking strategy to address anticipated stressors or hardships, and it will be measured by the Proactive Coping Subscale of the Proactive Coping Inventory (PCI). We hypothesized that proactive coping would serve as a moderator of the consequences of stress. The Proactive Coping Subscale of the PCI consists of 14 items that combine autonomous goal setting with self-regulatory goal attainment cognitions and behavior. The scale showed high internal consistency, as seen in reliability measures of .85 and .80 in two samples during its development [44,45].

Burnout

Burnout will be assessed by the Oldenburg Burnout Inventory (OLBI). Burnout is a psychological condition that follows highly demanding or stressful physical and mental work conditions that may be accompanied by inadequate resources [15,46]. Historically, the most commonly used instrument is the Maslach Burnout Inventory [47], which has been criticized on psychometric grounds because all items in each subscale are unidirectional [15]. We chose the OLBI because it avoids this problem by including positively and negatively framed items in the assessment of exhaustion and disengagement, which are two core features of burnout [15]. Moreover, the OLBI includes a stronger assessment of the cognitive aspect of work, which plays an important role in numerous health care functions. Data from the OLDI are also available from previous studies of health care workers [15].

Eating Habits

Increased caloric intake is a common response to mental stress [48]. We chose the brief, 7-item Loss of Control Over Eating Scale (LOCES) [49] to evaluate eating habits, as it maintains a good fit to the data analyzed by the original, 24-item LOCES [50]. The quality of the diet is as important as the caloric intake. We used a 2-question assessment of fruit and vegetable intake that has high specificity, based on correlations with biomarkers

in the test population (plasma ascorbic acid, beta carotene and alpha tocopherol 24-hour urinary potassium excretion) [51].

Morphometrics

Self-reported height and weight were obtained. Weight discrimination history, namely whether the participant experienced any bias based on body weight, was assessed by a single question [41,42].

Alcohol and Substance Use

We hypothesized that alcohol and substance use may increase in response to the stress of workplace demands, but we thought that a thorough screening would not be in the best interest of the overall study. We decided to limit our data to answers to two questions, namely, whether the participants' alcohol and substance use increased, was unchanged, or decreased since the start of the pandemic.

Physical Activity

We chose to assess physical activity with two brief questions: one on the amount of time the participants spent in moderate-to-vigorous physical activity, and one on whether their amount of physical activity had changed since the pandemic.

Health History Checklist

The relationship among stress, major life events, and other biopsychosocial factors has a long history of study in epidemiology and public health, with a sound mechanistic basis [52,53,54]. We hypothesized that the effects of working in the challenging circumstances of the COVID-19 pandemic would have effects on health over time. We obtained a comprehensive history of the participants' mental and physical health during the pandemic to enable prospective evaluation of incident conditions.

Exposure Assessment

We will define and quantify exposure to COVID-19 service burden by summing participants' scores on the Perception of Stress at Work scale developed by Wu and colleagues [4] in 2009 during the SARS pandemic, and we will add a point to that score for each of several additional stressors: (1) working more hours since the pandemic; (2) working in a different setting; (3) caring for patients with COVID-19; (4) changing one's living arrangement; (5) receiving a COVID-19 diagnosis; and (5) having a close contact (friend, family member, colleague, or any loved one) with a COVID-19 diagnosis (Table 2).

For this purpose, perceived stress was deemed to be an outcome of exposure, but it can also be included as an exposure variable in models that ascertain incidence of health conditions over time.

Table 2. Components of the algorithm-based score for exposure to COVID-19 service burden.

Component	Scoring
Perception of Stress at Work scale	Score of 9-item scale
Working more hours	Yes=1 additional point
Working in a different setting	Yes=1 additional point
Caring for patients with COVID-19	Yes=1 additional point
Changing one's living arrangement	Yes=1 additional point
Receiving a COVID-19 diagnosis	Yes=1 additional point
Having close contact (friend/family member/colleague/any loved one) with a COVID-19 diagnosis	Yes=1 additional point

Annual Follow-up Questionnaires

Annual follow-up questionnaires will include incidence of conditions and diseases, as well as selected instruments from the baseline and 6-month follow-up questionnaires. Additional items may be added in response to the evolving research literature on COVID-19 and that in other fields. Table 1 provides the anticipated data collection schedule.

Registry and Ancillary Studies

During enrollment participants were given the option of providing contact information for follow-up questionnaires, which also enrolls them in the CHAMPS Registry. The CHAMPS Registry enables recruitment of eligible individuals for clinical trials of interventions relevant to COVID-19 or other disorders or conditions, as well as for ancillary studies of basic behavioral research or observational studies that require new data collection. Anticipated ancillary studies include a detailed assessment of lifestyle factors, interactions with family life, and wellness interventions. Ancillary study proposals will be reviewed by the CHAMPS Steering Committee for relevance, scientific interest, and participant burden.

Analysis

Data Management and Quality

Data are collected through the web-based Qualtrics system. SPSS (IBM Corporation) and SAS (SAS Institute, Inc) will be used for data analysis. Initially, we will perform an exploratory analysis to establish patterns of missingness and distributions of the variables being measured. The registry data will be characterized with descriptive analyses, including frequency distributions, prevalence rates of COVID-19 testing and SARS-CoV-2 infection, and means and standard deviations of scores on the scales measuring work environment, general health status, anxiety, depressive symptoms, social support, traumatic

stress, social support, sleep quality, and stress. Multiple logistic and linear regression methods will be used to assess baseline associations of health and well-being with estimates of exposure to COVID-19 infection and COVID-19–related stress at work. Models will be adjusted for sex, age, race/ethnicity, and job classification. Other preliminary explorations of associations between measured variables will be performed to aid the development of substudies from the registry. Follow-up health status questionnaires will enable analysis of associations between incident health events and baseline variables.

Narrative responses to the final question on the questionnaire will be analyzed using a deductive approach and thematic content analysis techniques. Multiple investigators will read the narratives provided by participants to perform coding of the significant statements made by participants. After multiple readings, investigators will generate data categories and clusters of statements and will develop themes.

Aim 1

We will determine whether essential workers with higher COVID-19 service exposure burden will experience higher rates of stress, depression, anxiety, and substance use than the general population at the time they enroll in CHAMPS, and higher than in similar populations before the COVID-19 pandemic. We will compare exposure by type of service, occupation, and place of service (eg, clinical setting or community), controlling for age, self-reported sex, and race. We will conduct analyses to identify mediators, such as racial status, and moderators, such as proactive coping and resilience.

Aim 2

We will determine whether the severity of mental health symptoms will be associated with changes in the prevalence of SARS-CoV-2 infections by geographic region.

Aim 3

We will ascertain whether exposure to COVID-19 service burden will affect physical and mental health over time and how these are influenced by psychosocial variables (eg, stress, depression, anxiety, burnout). We will analyze whether longitudinal health outcomes are associated with type of service; severity and duration of mental health symptoms; and age, sex, race, and other variables. We anticipate that some analyses will depend on the adequacy of the sample sizes in various demographic subgroups.

Aim 4

We will obtain longitudinal data to determine whether mental health symptoms will persist longer among participants with more severe symptoms and whether these symptoms will be associated with higher incidence of physical health conditions.

Aim 5

We will ascertain the extent to which the thematic contents of the narrative responses to the final question of the questionnaires are correlated with measures of distress (stress, anxiety, depression, burnout) and moderated by measures of resilience. We will ascertain whether thematic content is a moderator or mediator of health outcomes and is associated with retention of participants over time.

Results

A review of the published literature on relationships between stressful life events and health led to the hypothesis that stress experienced by essential workers during the COVID-19 pandemic would affect their health status over time. In response, CHAMPS was designed to ascertain work-life experience during the first year of the pandemic, exposure to stress, and self-reported mental and physical health, as well as to determine effects of service during the pandemic on health over the subsequent 5 years. The CHAMPS longitudinal cohort serves as a registry for recruiting participants in future ancillary studies. After IRB approval, 2762 participants were enrolled between May 2020 and June 2021, with 1534 providing contact information for future studies and follow-up questionnaires.

Discussion

Principal Considerations

The longitudinal CHAMPS Study and Registry will provide important prospective data about relationships between extended health care–related service during a global pandemic and the future health of the health care–related workforce. Of special interest are first responders and service workers, who are less often included in such studies, as well as a broad ethnic diversity of participants. The lengthy enrollment period as the pandemic progresses should result in a sample with a wide range of exposures to various working conditions, thereby providing insights into the potential attributes that contribute to changes in health over time. Assessments of an extensive range of psychosocial factors, such as lifestyle habits, resilience, and pre-existing conditions, will enable assessment of their influence on mental and physical health.

The CHAMPS Registry is designed to provide opportunities for investigating additional questions and potential extension of data collection for specific hypotheses. The CHAMPS Registry anticipates ancillary studies of behavioral and biological mechanisms of action, studies of lifestyle changes and health, the effects of the pandemic on extended families, and potential randomized trials of interventions.

Altogether, CHAMPS has the potential to provide advances in knowledge about the role of chronic stress in health. The value of the study for some questions, such as identification of associations with various demographic variables, depends on the availability of a sufficient sample size of participants. We anticipate that over time, the study findings will inform public health policy relevant to national health emergencies.

Limitations

This is a convenience sample, which limits the generalizability of the results to the entire population of essential workers. Some occupation categories will have small sample sizes; thus, we may not have sufficient representation for individual analyses. Self-selection bias may also be a factor if some individuals decline to participate due to reluctance to be perceived as not

supportive of their institutions. The measurement of COVID-19 service exposure relies on an algorithm that should be evaluated against an independent data set. Finally, the planned longitudinal analyses will depend on retaining a sufficient proportion of participants over time.

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Authors' Contributions

The CHAMPS Study Investigators are as follows: coprincipal investigators: PGK, PhD; DSH, PhD, RN, FAAN; JLM, PhD, FAED; coinvestigators: PKB, PhD, RN, FAAN; HMB, PhD, RN, NP-C; LCC, PhD, RN, PMHCNS, BC, CNE, ANEF, NCC, CGP, FAPA; AC, MS; CD, MSN, RN; JDD, MSN; LM, PhD, RN; ABM, MSN, RN; SCS, EdD, RN, FAAN; and JY, PhD, RN, FAAN; data analysis core: JLM, AC, Robert L Sando, MGA, and Mu-hsun Chen, BA; lifestyle study: Tracy L Oliver, PhD; Rebecca Shenkman, MPH; and Lisa K Diewald, MS; family health study: LCC; Janette E Herbers, PhD; Michelle McKay, PhD, RN, CCRN; Amy McKeever, PhD, RN, CRNP, WHNP-BC; Helene Moriarty, PhD, RN, FAAN; Michelle M Kelly, PhD, CRNP, CNE; and Christine A Pariseault, PhD, RN (Widener University), Abigail Knight MSN student and Isabel Mahan, BSN student; biofeedback study: JLM; Guy M Weissinger II, MPhil, PhD, RN; Mary Ann Cantrell, PhD, RN, CNE, ANEF, FAAN; Rachel Baskin, MSN, RN, CPN; Cerena George, MSN; Alexis Cohn, BSN student and Rachel Randall, BSN student.

Conflicts of Interest

None declared.

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Abbreviations

BRS: Brief Resilience Scale
CHAMPS: COVID-19 Study of Healthcare and Support Personnel
GAD-7: Generalized Anxiety Disorder-7
IES-R: Impact of Events Scale - Revised
IRB: Institutional Review Board
ISI-7: Insomnia Severity Index-7

LOCES: Loss of Control Over Eating Scale
OLBI: Oldenburg Burnout Inventory
OSSS-3: Oslo Social Support Scale-3
PCI: Proactive Coping Inventory
PHQ-2: Patient Health Questionnaire-2
PTSD: posttraumatic stress disorder
SARS: severe acute respiratory syndrome

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Protocol

Evaluation of Novel Concentrated Interdisciplinary Group Rehabilitation for Patients With Chronic Illnesses: Protocol for a Nonrandomized Clinical Intervention Study

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Abstract

Background: An aging population with a growing burden of chronic complex illnesses will seriously challenge the public health care system. Consequently, novel and efficacious treatment approaches are highly warranted. Based on our experiences with concentrated treatment formats for other health challenges, we developed a highly concentrated interdisciplinary group rehabilitation approach for chronic illnesses.

Objective: We aim to explore the acceptability of the intervention and describe potential changes in functional impairment at follow-up.

Methods: The cornerstones of the intervention are as follows: (1) prepare the patient for change prior to treatment, (2) focus on health promoting microchoices instead of symptoms, and (3) expect the patient to integrate the changes in everyday living with limited hands-on follow-up. The intervention will be delivered to patients with highly diverse primary symptoms, namely patients with low back pain, post–COVID-19 symptoms, anxiety and depression, and type 2 diabetes.

Results: Recruitment started between August 2020 and January 2021 (according to the illness category). For initial 3-month results, recruitment is expected to be completed by the end of 2021.

Conclusions: If successful, this study may have a substantial impact on the treatment of low back pain, post–COVID-19 symptoms, anxiety and depression, and type 2 diabetes, which together constitute a major socioeconomic cost. Further, the study may widen the evidence base for the use of the concentrated treatment format in a diverse group of medical conditions.

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KEYWORDS

COVID-19; chronic illnesses; concentrated rehabilitation; low back pain; post–COVID-19 symptoms; post–COVID-19 syndrome; long COVID; fatigue; type 2 diabetes; anxiety; depression

Introduction

Background

An aging population with a growing burden of chronic complex diseases seriously challenges the ability to deliver adequate health services [1-3]. Adding to this, the ongoing COVID-19 pandemic has resulted in a new group of patients, who, having recovered from the acute infection, may experience a range of long-lasting symptoms. This hitherto unknown condition is frequently termed post–COVID-19 syndrome (or long COVID) and may also affect people in whom the primary infection was mild [4,5]. If we do not succeed in delivering treatment that enables patients to deal effectively with their long-lasting illnesses, the public health care system is unlikely to cope with the upcoming demographic challenges [6,7].

Although patients with chronic illnesses have a wide range of symptoms, pain and fatigue are among the most common [8,9]. Medical advice typically encourages the patient to be as active as possible, eat healthily, get enough sleep, avoid stress [10-12], and monitor improvement or worsening by using medical diaries and symptom logs [13]. Since the patient's main concern is to prevent worsening of the condition, activities that might increase symptoms are typically avoided [14]. Examples of such behavior patterns can be to restrict physical activity upon muscle pain; to stand, walk, or move carefully; to rest or sleep whenever feeling exhausted or tired; and to rest before or after engaging in activities. Over time, such coping strategies are likely detrimental and might contribute to conservation or worsening of symptoms. This is especially the case when the first indication of improvement might be a temporary worsening of symptoms, such as muscle pain or tiredness after increased physical activity.

Based on extensive experience with concentrated treatment formats [15-19], we have developed a comprehensive transdiagnostic rehabilitation for chronic illnesses, characterized by a systematic focus on how to initiate and maintain change. In the presently described protocol, this intervention will be piloted on patients with a diversity of chronic health challenges, including chronic low back pain, post–COVID-19 symptoms, anxiety and depression, and type 2 diabetes. These conditions were chosen as they collectively represent major personal and societal costs [20]. Furthermore, the included disorders are characterized by fundamentally different symptoms and challenges (eg, pain, fatigue, depression, anxiety, dyspnea, and glucose variability). In consequence, we are able to summarize the overall effectiveness of the intervention across disorders, in addition to illness-specific outcomes. Finally, by including patients with post–COVID-19 symptoms (fatigue, dyspnea, problems with concentration, diurnal patterns, and/or nutrition), we may be able to further advance this field, as there presently are large knowledge gaps concerning the long-term prognosis and natural development of the complaints [21].

One of the main features of this novel cross-disciplinary concentrated intervention (lasting less than a week) is a shift in focus from targeting symptoms to targeting and monitoring everyday microchoices that facilitate increased levels of functioning. The intention of these microchoices is to break inflexible patterns of symptom regulation by "doing something different" whenever tempted to be guided by the symptoms. This approach enables the patient to systematically increase flexibility and their levels of functioning when symptoms and health challenges are present. In addition, a focus on deliberate behavior instead of symptoms implies that change is within reach and possible to control [17,22].

In order to ensure a safe setting in which participants may challenge their current coping strategies, they will work together with an interdisciplinary team, and each patient will design individually tailored plans for the most relevant microchoices. To ensure that the patients are prepared to initiate change, they are thoroughly introduced to the program prior to treatment, and if reluctant or unable to dedicate their full attention, they are encouraged to postpone participation until ready. After the concentrated intervention, the patients will be prepared to integrate the changes as part of their everyday living.

The aim of this pilot study is to explore the acceptability of the concentrated interdisciplinary group rehabilitation for patients with chronic low back pain, post–COVID-19 symptoms, anxiety and depression, and type 2 diabetes, and to describe the basic changes in functional status. Based on our experiences with other concentrated treatment formats, we expect the intervention to be highly acceptable and to have significant effects on functional impairment [15-19].

Main Hypotheses

We hypothesize that the treatment will be acceptable as indicated by the following [22,23]:

1. Proportion (≥90%) of patients who meet the inclusion criteria and accept participation.
2. Proportion (≥90%) of included patients who attend the concentrated intervention.
3. Proportion (≥90%) of included patients who complete participation in the concentrated intervention.

Further, we hypothesize that patients will be satisfied with the treatment, as defined by a mean Client Satisfaction Questionnaire (CSQ) score of 20 or more, and with no single dimension below an average score ≤2. A cutoff score of 20 has been chosen based on previous research using scores ≥20 to indicate "good" satisfaction [24].

Finally, we hypothesize that the patients' levels of functioning will be improved at follow-up as measured with the Work and Social Adjustment Scale (WSAS), and that there will be a significant change in how much the illness affects the patients' life as measured with the Brief Illness Perception Questionnaire (BIPQ) in the following domains:

1. How much does your illness affect your life?
2. How much control do you feel you have over your illness?

3. How concerned are you about your illness?
4. How well do you feel you understand your illness?

We do not anticipate significant changes in the following domains for all 4 included illnesses:

1. How long do you think your illness will continue?
2. How much do you experience symptoms from your illness? How much do you think your treatment can help your illness?
3. How much does your illness affect you emotionally? (eg, does it make you angry, scared, upset, or depressed?)

Methods

Overview

This pilot study is part of the "Project Development of Smart Health Solutions" (PUSH project), a collaboration between Haukeland University Hospital (Bergen, Norway) and Helse i Hardanger (Øystese, Norway). The overall aim of the PUSH project is to develop more efficient and cost-effective treatments to be integrated as part of public health care. The project is headed by a steering committee at Haukeland University Hospital, whereas the interventions and study data collection are primarily done at Helse i Hardanger, a health care research facility located outside Bergen.

Study Design and Participants

This study is designed to test the acceptability of concentrated interdisciplinary group rehabilitation with an open pre-post follow-up design in the following 4 groups of patients with chronic illnesses: chronic low back pain, post–COVID-19 symptoms, anxiety and depression, and type 2 diabetes. The treatment will be delivered in groups of 6 to 10 patients, and the initial pilot study will include between 40 and 50 patients for each illness (4-6 treatment groups for each illness). For the inclusion and exclusion criteria, please refer to Textbox 1, and for the overall study flowchart, please refer to Figure 1.

Textbox 1. Inclusion and exclusion criteria.

For all diagnoses

Inclusion criteria

- Fluent in oral and written Norwegian
- Access to a smartphone and sufficient digital competence to handle online questionnaires
- Negative COVID-19 polymerase chain reaction test

Exclusion criteria

- Cognitive failure
- Lack of self-reliance in daily routine
- Severe mental health problems preventing engagement in the rehabilitation program
- Conditions that inhibit physical activity

Chronic low back pain

Inclusion criteria

- Low back pain with or without radiculopathy
- Age between 18 and 70 years
- Low back pain >3 months, and at least 4 months of sick leave
- Ability to participate in a group-based posttreatment physical training in Bergen, Voss, or Kvam municipalities

Exclusion criteria

- Surgery during the last 8 weeks
- Available alternative rehabilitation therapy for low back pain

Type 2 diabetes

Inclusion criteria

- Type 2 diabetes
- Age >18 years
- Presence of at least one of the following complications/challenges:
  - Dysglycemia
  - Frequent or severe hypoglycemia
  - Weight gain
  - Diabetes complications
  - Diet, physical activity, and/or medical treatment challenges

Exclusion criteria

- Type 1 diabetes
- Monogenic diabetes
- Secondary diabetes (pancreatogenic or any other form of secondary diabetes)
- Ongoing pregnancy

Post–COVID-19 symptoms

Inclusion criteria

- Age between 18 and 67 years
- >2 months since the COVID-19 infection
- Impaired ability to work full time
- Substantial post–COVID-19 physical and/or mental health problems

- Fatigue
- Dyspnea
- Concentration difficulties
- Sleeplessness, diurnal disturbances
- Nutritional deficiencies

Exclusion criteria

- Exercise contraindication

Anxiety or depression

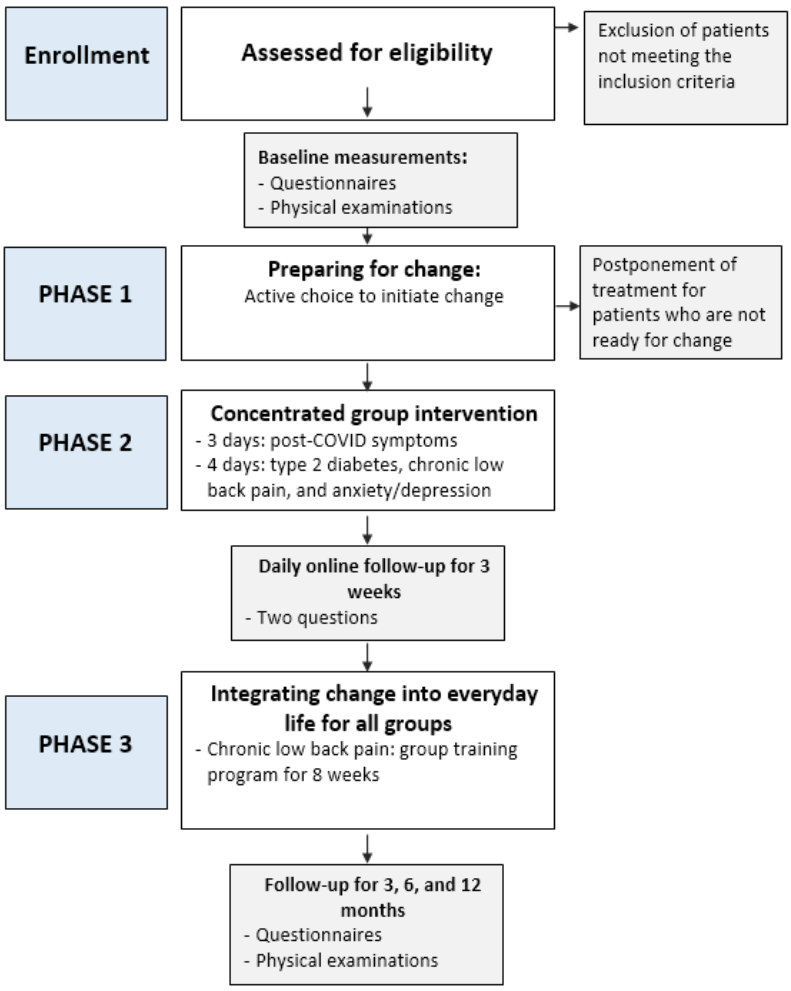
Inclusion criteria

- Age between 18 and 47 years
- Fulfilling ICD-11 criteria for one of the following disorders:
  - Mixed anxiety and depressive illness
  - Other mixed anxiety illnesses
  - Unspecified anxiety illness
  - Generalized anxiety illness
  - Depressive episode
  - Recurrent depression
  - Unspecified recurrent depression

Exclusion criteria

- Bipolar illness
- Psychosis
- Ongoing substance abuse/dependence
- Ongoing suicidal ideation

Figure 1. Flowchart of the study. With regard to illness-specific physical exercise tests and examinations, evaluation was performed with questionnaires at pretreatment, and 1-week and 3-, 6-, and 12-month follow-ups. The 2 questions were as follows: To what extent did you allow the symptoms to decide today (0-10) and To what extent did you make use of the principle of doing something else (0-10).



Procedures and Patient Flow

Although patients themselves may initiate the process, all potential participants need to be referred by their general practitioner or other physician responsible for the treatment of the relevant condition. If the patient fulfills the inclusion criteria, they will be invited to sign the informed consent and offered participation in the project successively upon availability in the groups.

One of the clinicians will call the patients upon referral and check the inclusion/exclusion criteria. During this phone call, the patients will be informed about the PUSH project and that the intervention is a concentrated interdisciplinary group treatment that will take place in Øystese, outside Bergen. If they fulfill the inclusion criteria and none of the exclusion criteria, an appointment for screening will be made. Before they answer the online questionnaires, they will be asked to watch videos describing the program, to ensure that all participants receive the same information (at the homepage [25]). For low back pain and type 2 diabetes, the informed consent will be signed online, while patients with post–COVID-19 symptoms or anxiety/depression will sign at baseline testing, when the first face-to-face meeting takes place. For low back pain and type 2 diabetes, participants will be invited in groups for an approximately 2-hour meeting 1 to 3 weeks before the treatment to make sure they are prepared for the intervention. For patients with anxiety and depression, or post–COVID-19 symptoms, the same information will be provided individually during the screening. All patients will be contacted by a therapist during the week prior to the treatment to confirm that they have received all necessary information and are ready to start their concentrated rehabilitation.

Outcomes

Assessments will be performed before and 1 week after the concentrated rehabilitation program, and after 3, 6, and 12 months. An overview of the measurement tools and the respective assessment times are presented in Table 1. The outcomes are selected with the aim of describing the overall experiences with the concept of the concentrated treatment format. More detailed disease-specific outcome measures will also be assessed, but will not be presented in this generic protocol paper, as they pertain to other aspects than the concentrated treatment format per se. The initial results will be published following 3 months of follow-up, whereas the final results are to be published upon 12 months of follow-up.

Table 1. Questionnaires and clinical and physical examinations.

Questionnaires and assessments	Assessment point
Client Satisfaction Questionnaire	One week after rehabilitation
Brief Illness Perception Questionnaire	Baseline, and 1 week and 3, 6, and 12 months after rehabilitation
Work and Social Adjustment Scale	Baseline, and 3, 6, and 12 months after rehabilitation
Strategies for handling symptoms (rating 0-100 and 2 questions[a])	Daily reports for 21 days after rehabilitation
Bergen Insomnia Scale	Baseline, and 1 week and 3, 6, and 12 months after rehabilitation
Patient Activation Measure	Baseline, and 1 week and 3, 6, and 12 months after rehabilitation
EQ-5D-5L (EuroQOL)	Baseline, and 3, 6, and 12 months after rehabilitation
Consumption of health care	Baseline, and 3, 6, and 12 months after rehabilitation
Medication lists	Baseline, and 3, 6, and 12 months after rehabilitation
Body weight/BMI	Baseline, and 3, 6, and 12 months after rehabilitation

[a]To what extent did you allow the symptoms to decide today (0-10) and To what extent did you make use of the principle of doing something else (0-10).

Primary Outcome Measures

Acceptability

The acceptability of the treatment will be measured by the following variables: (1) The proportion of patients accepting to participate in the treatment among those fulfilling the inclusion criteria and offered participation; (2) The proportion of patients offered participation who start treatment; and (3) The proportion of patients completing the treatment program (on-site).

CSQ

The CSQ-8 is an 8-item questionnaire that measures patient satisfaction with health services, where the items are rated from 1 (very low satisfaction) to 4 (very high satisfaction) [26]. The total score ranges from 8 to 32, with higher scores indicating higher degrees of satisfaction. The CSQ-8 has good psychometric properties, with high internal consistency (Cronbach α=.93) and high interitem correlation [27].

BIPQ

The BIPQ is a 9-item questionnaire designed to assess cognitive and emotional representations of illness [28]. Questions are graded from 1 to 10. The last item deals with the perceived cause of illness, in which respondents list the perceived 3 most important causal factors in their illness. For this questionnaire, the general word “illness” can be replaced by the name of a particular illness. The word “treatment” in the treatment control item can be replaced by a particular treatment such as “surgery” or “physiotherapy.” The scale has good psychometric properties according to a recent review [29].

WSAS

The WSAS is a short questionnaire measuring the impact of the illness on aspects of work and social activities [30]. The scale consists of five items rated from 0 (not at all) to 8 (very severe), and a higher score indicates higher impairment (maximum score is 40). The scale is regarded as reliable and valid, with good psychometric properties.

Transdiagnostic Secondary Outcome Measures

At pretreatment and posttreatment, and the follow-up assessments, the patients will be asked to rate on a scale from 0 to 100 to what extent they use the following strategies when trying to handle the symptoms: (1) Wait to start an activity until I feel up to it; (2) Wait to start an activity until I am certain that I will succeed; (3) Ensure that the symptoms will not get worse; (4) Ensure that I am prepared to handle challenges; (5) Try to calm down before proceeding when I get anxious; (6) Spend a lot of time on worrying and ruminating; (7) Avoid socializing if I do not feel up to it; (8) Ensure that I get enough rest; (9) Try to not let others see how I feel; (10) Try to have a positive mindset; and (11) Follow my gut feeling. The questionnaire was developed in cooperation with patients having previous experience in the concentrated treatment format.

Intervention

The intervention consists of the following 3 equally important phases (Figure 1): (1) Preparing for change, (2) The concentrated intervention, and (3) Integrating change into everyday living. Throughout the intervention, the focus is on how to initiate and maintain change by utilizing discomfort as a guide to break inflexible patterns of symptom regulation. By intention, the topics introduced in the different phases overlap considerably. In order to incorporate the central aspects of a given health challenge, minor illness-specific adaptations are made to the intervention.

Phase 1: Preparing for Change

It is essential that the patients are thoroughly informed and prepared prior to the rehabilitation, and that they have made an active choice to initiate change. During the pretreatment information meeting, the topics below will be covered using nontechnical terms and easily understandable metaphors (with slight illness-relevant modifications).

Improved Everyday Functioning

The goal of this program is to help the participant to live a life where the symptoms/health challenges do not decide how the

person behaves. Thus, it is a program focused on change, with the goal of a better life and improved everyday functioning.

Challenge Patterns of Symptom Regulation

Living with a chronic illness implies that patients are continuously trying to prevent their health from getting worse, which makes sense. However, one of the consequences might be that the patients develop patterns of symptom regulation that might contribute to conservation or, in some instances, might exacerbate the problem. Typically, the patient finds it hard to know when to be cautious and when to challenge a given strategy to deal with the symptoms. In our experience, people with chronic illnesses typically have an adequate understanding of their problems, but this does not necessarily lead to change. It may rather increase the feeling of helplessness because they do not know how to initiate and sustain change. The concentrated treatment is a practical deliberate approach focused on how to identify and break unhelpful patterns of symptom regulation.

Therapist-Assisted Behavior Activation

In line with the above, the illness is frequently a composite of health challenges that might require expertise from a number of specialized professions. During 4 consecutive days (3 for post–COVID-19 symptoms), a highly qualified interdisciplinary team will provide practical information and hands-on coaching while the patients challenge the way symptoms are handled. Patients referred to the program for anxiety and depression are, prior to treatment, expected to provide suggestions regarding unhelpful patterns of regulation, which they are willing to start changing during the concentrated treatment days (eg, avoidance of specific situations, social withdrawal, etc).

Group Setting

The concentrated treatment is delivered in groups of 6 to 10 patients. The participants will work side by side and challenge their own expectations regarding what they are capable of doing. In the group setting, each participant will need to take responsibility for making the treatment sessions relevant for their specific problems.

Basic Bodily Rhythms

An important aspect of the treatment is a focus on the practical implications of bodily rhythms such as sleep-wakefulness, activity-rest, and meal habits.

Substantial Self-Effort

All participants are expected to stay at the adjacent hotel throughout the treatment week in order to dedicate full days to the treatment and engage in all parts of the program from 8:30 AM to 4:00 PM. On the last day, the program will be finished after lunch. From 4:00 PM to 7:00 PM, each participant will practice on their own based on what they learned during the treatment. This means that there will not be room for other appointments during the concentrated intervention period, and their full focus will be on changing their unhelpful behavior patterns.

Start Planning Life After the Concentrated Intervention

Since the focus is to increase the level of functioning, it is necessary that each participant, prior to the treatment week, decides upon how to practice the changes and integrate them into their lives, starting directly after returning home. This includes specific plans to increase participation at work/school or other activities that will lead to better daily functioning.

No Participation Until Ready

No treatment or medicine works if the patient is not willing to take it. This is even true for penicillin. If the patients are reluctant to participate, we will recommend waiting until they are ready to make a change.

An adapted version of the Borkovec and Nau *Reaction to Treatment Scale* is used to explore the patients' readiness for treatment [31]. A low rating (<70%) on any of the 4 questions ("How much does this approach make sense?" "How likely is it that you would recommended this treatment to a friend with similar problems?" How likely is it that you will be fully engaged in the program?" "How likely do you think it is that you will benefit from the program?") will serve as an opportunity to clear up any misunderstandings and, together with the patient, decide if it might be better to postpone treatment initiation.

Phase 2: The Concentrated Group Intervention

The program starts with patient education, and the most important points will be repeated throughout the week. At the first session, rules of confidentiality will be established. During the first part of day 1, each participant will provide some information about his/her health problem based on the following: "How long have you struggled with this health challenge?" "What does it prevent you from doing?" "What are you looking forward to do when this is no longer a problem?" The participants will use 2 to 3 minutes each. Patient education will be interspaced with physical activity, brief mindfulness sessions, and practical training sessions focused on breaking problematic patterns of symptom regulation

Transdiagnostic Elements of the Group Intervention

Patient Education

Patient education will be provided on how to initiate and maintain relevant change and, at the same time, accept those things that cannot be changed or controlled (eg, history, thoughts, and feelings [for post–COVID-19 symptoms and type 2 diabetes: getting the infection/having the illness]). It will be underscored that change starts with an active decision and that the goal of the treatment is to increase flexibility and to live a life where the symptoms do not decide.

Microchoices

Microchoices will be used as a term that refers to the moments when you discover specifically how and where in your everyday life the symptoms are making choices on behalf of you, and where you have an option to choose differently. Participants will be encouraged to do things they have avoided in fear of symptom worsening. It will be emphasized that change is measured in behavior (what you do) and *not* in the reduction of symptoms. Symptom reduction, on the other hand, will be described as a positive and valuable side effect of behavioral change. This shift in focus from symptoms to deliberate behavior implies that change is within reach. Furthermore, participants

will be challenged to do a value-based microchoice each day, for example, call a friend or relative whom they had neglected due to the health problems. During patient education, this concept is introduced and explained (ie, having health problems and symptoms may make people more self-centered and lose perspective, making them lose track of who they were, and value-based actions may help them get back on track and widen their focus).

Individually Tailored Practice

Individually tailored practice in discovering microchoices and "breaking problematic patterns" in as many relevant settings as possible will be the cornerstone of each day.

Feedback and Coaching

Each morning, at lunchtime, and at the end of the joint program, everyone will be asked to share their self-evaluation on how successful they have been in identifying their own patterns of symptom regulation, and to what extent they have attempted to break the patterns. A scale from 1 to 6 will be used. If they rate themselves lower than a 6, the group leader will explore the reasons for this, with the aim of helping them find the moments of "microchoices" and identify what they can do to break the pattern. Throughout these sessions, symptoms will not be given attention, but rather described as being important, in order to be able to identify targets where it might be possible to break the patterns of regulation.

Physical Activity

These sessions will vary across illnesses; however, common for all participants will be instructions to attempt making the physical activity relevant for their own challenges and fit into their projects of "breaking patterns of symptom regulation." For some, this might mean to refrain from the temptation to overdo, and for others, it might imply to be more active or active in a different way. For patients with anxiety/depression, the task during the physical activity will be to "surprise themselves" by doing a little more when they feel they have reached their limit. Patients with low back pain will follow the validated ready-to-use program "GLA:D Back," integrating patient education and exercise therapy [32,33]. For post–COVID-19 patients, the physical training will be a mix of high- and low-intensity training, focusing on increased exercise capacity and the restoration of trust in one's own body. In the type 2 diabetes group, the main aim will be to experience how a diverse range of activities can be useful in order to maximize the effect of the body's available insulin.

Mindfulness

Each day will contain one to three brief sessions of detached mindfulness, where the task will be to focus on breathing, while at the same time observe (and accept, without trying to change) wandering thoughts, bodily sensations, etc [34].

Food and Meal Habits

One of the patient education sessions will be focused on useful dietary choices. For patients with post–COVID-19 symptoms affecting diet and/or nutrition, the focus will be on useful dietary choices with a focus on helping the body to recover. In patients with anxiety and depression, the focus will be on the establishment of good mealtime habits as a way of restoring diurnal rhythms. For patients with type 2 diabetes, the emphasis will be to explore how to get the maximum out of the available insulin (ie, their beta-cell capacity or their insulin injections). During this session, they will also test different "forbidden" (carbohydrate-rich) food items and evaluate the consequences on their blood glucose levels. This will be followed by physical activity to experience the restoration of habitual glucose levels. The aim is to recognize that no food is forbidden, but that there are consequences of the choices, with various possible compensatory actions.

Pharmacist

For all participants, a pharmacist will review the individual medication lists, focusing on potential harmful interactions. In the low back pain group, 2 sessions of patient education are provided. The first session is on various types of formulations and medications in general, followed by an illness-specific session focusing on the risks of combining pain medications, the potential impact on driving capabilities, and an overall emphasis on minimizing the use of opioid-based and other pain-relief symptom treatments. Individual advice on the downsizing and discontinuation of medication is provided in cooperation with the study physician. Following the same pattern, the type 2 diabetes group also has 2 interactive educative sessions with the pharmacist. Here, the second session deals specifically with diabetes medications (use, effects, and most common side effects). For patients with post–COVID-19 symptoms, a short patient education is followed by a brief counseling session with a pharmacist on the proper use of inhalators.

Afternoon Practice

Before the group splits at 4:00 PM each day, individual practice plans for each afternoon and evening will be made, focusing on implementing microchoices in terms of physical activity, social/value-based activity, self-reflection, etc.

Individual Consultation

During the program, all patients will receive an individual consultation with the group leader or one of the psychologists or psychiatrists who are experts on the concentrated treatment format. This consultation will be focused on how to integrate the change into everyday living.

Preparing for Life After the Treatment

By the end of the program, all patients will have made a specified plan addressing how to integrate the change into normal living using the concept of SMART (specific, measurable, achievable, relevant, time-bound) goals [35,36]. Moreover, they will start answering the following daily questions online: "To what extent did you allow the symptoms to decide today" (0-10) and "To what extent did you make use of the principle of *doing something else*" (0-10).

Phase 3: Integrating the Change Into Everyday Living

Daily Online Reports

For 3 weeks after the concentrated program, through a digital solution, all patients will answer the 2 daily questions (described above) pertaining to the maintenance of the change. This will

be done without feedback from the program. Helse i Hardanger is in the process of developing a smartphone app through which the patients are expected to answer questionnaires, store their SMART goals, and provide feedback. The program will facilitate contact with the clinic if needed.

Individual Video or Phone Consultation

Ten days after the concentrated treatment, an individual phone or video consultation is performed, focusing on how to maintain the change. Additionally, patients with low back pain follow the program for GLA:D Back, with training twice a week for 8 weeks at certified local GLA:D Back facilities.

Further Follow-Up and Data Gathering

All patients will answer questionnaires at 3-, 6-, and 12-month follow-ups. Further disease-specific examinations and/or data may also be gathered; however, the descriptions of these are outside the scope of this generic protocol paper.

Competency in the Concentrated Treatment Format

A psychologist with extensive experience with concentrated treatment formats will lead all groups for patients with anxiety/depression, and these groups will be used for hands-on training in the format for clinicians working with the other illnesses. The content of all manuals (standard operating procedures) is supervised and approved by the originator of the format (GK), and all groups will receive hands-on supervision daily from GK.

Statistical Analyses and Data Handling

Data will be analyzed with Stata version 17 (StataCorp). Changes in WSAS and BIPQ scores from pretreatment to posttreatment and the 3-month follow-up will be examined with repeated measures analyses. Statistical significance will be set at α=.05. Within-group effect sizes will be calculated using Glass' Δ, with pretreatment SD as the denominator. Glass' Δ is the recommended effect size for intervention studies, in which there are reasons to believe that the treatment will influence the SD as well as the mean [37]. An effect size is commonly interpreted as small (0.2), moderate (0.5), or large (0.8). Considering that this project is a pilot study of a novel interdisciplinary group treatment and that both the WSAS and BIPQ are global and not condition-specific measures, we expect the effect sizes to be small to moderate in magnitude.

Missing data on the primary outcome variables will be handled by multiple imputation (MI). Under the *missing at random* (MAR) assumption, MI is currently one of the best available methods of dealing with missing data and will provide unbiased estimates [38]. The main analyses of the primary outcomes will thus be conducted under the assumption of MAR. Sensitivity analyses will be conducted to assess the robustness of the results and the potential impact that nonignorable missingness may have on the estimated results. These sensitivity analyses will take a pattern-mixture approach [39]. In short, a pattern-mixture approach can involve assuming that participants who are lost to follow-up have a mean outcome that differs from that of participants who do not drop out by an offset. The impact on the results of various choices of clinically plausible offsets can then be examined, and if the effect from the primary analysis is qualitatively maintained for the range of plausible offsets, the findings can be said to be robust.

Data Collection and Monitoring

For each illness, a centralized team will be established. This team will have monthly contact with a designated researcher for each illness in order to monitor inclusion and data collection. Most of the data will be collected electronically, and all sensitive data will be stored on an encrypted server at Helse Vest IKT. Once the patients are included, all data entered by them will be monitored by the Study Administrative Team, as part of clinical follow-up.

Adverse Events

If an acute condition occurs, the patients will receive the necessary care, and they might be excluded from the study if there are concerns about safety. Such patients will be thoroughly described and accounted for, in line with illness-specific standard operating procedures.

User Involvement

The project has established a broad user panel with representatives recruited through Haukeland University Hospital and Helse i Hardanger. The following organizations are represented: Norwegian Asthma and Allergy Association, Norwegian Rheumatics' Association, Mental Health Norway, Breast Cancer Association, Norwegian Diabetes Association, Norwegian Association for Lung and Heart Disease, and "Grannehjelpa" (neighbors' help). The panel has given feedback throughout the development of the protocol and has approved the final version.

Ethical Considerations

The PUSH project and the web application have been approved by the Research Ethical Board, Helse Vest (2020/101638), and the project will be conducted in accordance with the Helsinki Principles.

Gender Perspectives

The inclusion factors and all interventions are gender neutral. However, in order to ensure adequate external validity and proper representation, we have no absolute limits in terms of the minimum inclusion rates of one gender. For all illnesses, the project will aim for at least 30 to 70 representations of the genders.

Results

Recruitment started between August 2020 (anxiety/depression) and January 2021 (diabetes). For initial 3-month results, recruitment is expected to be completed by the end of 2021.

Discussion

Overview

In this paper, we describe a protocol for the establishment and initial evaluation of a novel concentrated interdisciplinary group rehabilitation for patients with chronic low back pain, post–COVID-19 symptoms, anxiety/depression, or type 2 diabetes. To our knowledge, this will be the first study to

evaluate concentrated interdisciplinary group rehabilitation for such a diverse range of chronic health issues. Based on previous experiences with the short concentrated treatment format, we hypothesize that the intervention described will be positively received by the participants, will reduce the impact of the illness on their lives, and will improve the level of daily functioning.

The study is designed with participants as their own controls (pre-post comparisons) with a 12-month follow-up. Although this allows for summarizing the experiences and findings as described above, causal conclusions on the effects of the intervention may not be drawn. However, in our mind, this is an essential first step enabling subsequent separate controlled trials where such research questions, as well as cost-effectiveness issues, may be addressed. Still, the modest labor factor (10 patients, 2 group leaders) clearly benefits our concentrated treatment format, if shown to be efficacious.

If the intervention is followed by meaningful improvements for the participants, we will be able to help large groups of patients with chronic illnesses to adhere to choices in their daily living that eventually will enhance their functional status. The fact that participants need only 3 or 4 days of sick leave to take part in the intervention owing to the concentrated format, with the continued rehabilitation process at home, is another clear advantage. Existing rehabilitation programs for chronic illnesses often have a duration of 3 to 4 weeks or longer and therefore require a longer time away from home and, for those who are working, longer sick leave. Another benefit of our intervention is the focus on implementing microchoices in everyday life, with guided practice during the intervention and assisted introduction into life at home and work. Although this needs to be investigated, the aim is to ensure the long-term maintenance of the new life trajectory.

Considering the methodology, dropouts and poor adherence to the intervention can threaten the internal validity. Although proper information aims to limit this problem, we cannot be sure that the participants will participate for the whole period or whether they will complete digital and clinical examinations at 3-, 6-, and 12-month follow-ups. A notice will be sent to the patients about 2 to 3 weeks before the assessments. Participants who do not answer the questionnaires online or do not show up for clinical follow-up will be contacted by telephone. The impact of missing data will be assessed with appropriate statistical methods (ie, multiple imputations and sensitivity analysis). Finally, although the acceptability of the treatment, as defined in this project, has been used in a number of publications with a concentrated treatment format, this outcome is not formally validated [22,23]. To compensate, all causes for not accepting, attending, or completing the intervention will be recorded.

This protocol describes a novel transdiagnostic rehabilitation approach, and the illnesses in focus are clearly disparate. Hence, if the intervention in the described study appears effective, it could trigger new studies investigating the effects on other chronic diseases or health challenges. In line with this and to facilitate potential dissemination of the concentrated rehabilitation format, a training program for relevant health professionals will be made available.

Conclusion

We present a protocol for the establishment and evaluation of a novel concentrated treatment to be investigated in patients with chronic low back pain, post–COVID-19 symptoms, anxiety/depression, or type 2 diabetes. The treatment focuses on how to initiate and maintain change, with a shift away from monitoring symptoms and toward an active approach to daily health-promoting microchoices. This short intervention has the potential of fundamentally changing the way we deliver health care to these patient populations, and hence, it could be a useful addition to the treatment armamentarium of the health care system, in the face of upcoming sociodemographic challenges.

Conflicts of Interest

SR is a shareholder of Helse i Hardanger. No other conflicts of interest are declared.

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Abbreviations

BIPQ: Brief Illness Perception Questionnaire
CSQ: Client Satisfaction Questionnaire
MAR: missing at random
MI: multiple imputation
PUSH project: Project Development of Smart Health Solutions
WSAS: Work and Social Adjustment Scale

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Protocol

Problems in Coordinating and Accessing Primary Care for Attached and Unattached Patients Exacerbated During the COVID-19 Pandemic Year (the PUPPY Study): Protocol for a Longitudinal Mixed Methods Study

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Abstract

Background: The COVID-19 pandemic has significantly disrupted primary care in Canada, with many walk-in clinics and family practices initially closing or being perceived as inaccessible; pharmacies remaining open with restrictions on patient interactions; rapid uptake of virtual care; and reduced referrals for lab tests, diagnostics, and specialist care.

Objective: The PUPPY Study (Problems in Coordinating and Accessing Primary Care for Attached and Unattached Patients Exacerbated During the COVID-19 Pandemic Year) seeks to understand the impact of the COVID-19 pandemic across the quadruple aims of primary care, with particular focus on the effects on patients without attachment to a regular provider and those with chronic health conditions.

Methods: The PUPPY study builds on an existing research program exploring patients' access and attachment to a primary care practice, pivoted to adapt to the emerging COVID-19 context. We intend to undertake a longitudinal mixed methods study to understand critical gaps in primary care access and coordination, as well as compare prepandemic and postpandemic data across 3 Canadian provinces (Quebec, Ontario, and Nova Scotia). Multiple data sources will be used such as a policy review; qualitative interviews with primary care policymakers, providers (ie, family physicians, nurse practitioners, and pharmacists), and patients (N=120); and medication prescriptions and health care billing data.

Results: This study has received funding by the Canadian Institutes of Health Research COVID-19 Rapid Funding Opportunity Grant. Ethical approval to conduct this study was granted in Ontario (Queens Health Sciences & Affiliated Teaching Hospitals Research Ethics Board, file 6028052; Western University Health Sciences Research Ethics Board, project 116591; University of Toronto Health Sciences Research Ethics Board, protocol 40335) in November 2020, Québec (Centre intégré universitaire de

santé et de services sociaux de l'Estrie, project 2020-3446) in December 2020, and Nova Scotia (Nova Scotia Health Research Ethics Board, file 1024979) in August 2020.

Conclusions: To our knowledge, this is the first study of its kind to explore the effects of the COVID-19 pandemic on primary care systems, with particular focus on the issues of patient's attachment and access to primary care. Through a multistakeholder, cross-jurisdictional approach, the findings of the PUPPY study will inform the strengthening of primary care during and beyond the COVID-19 pandemic, as well as have implications for future policy and practice.

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KEYWORDS

primary care; health services research; health policy; mixed methods research; COVID-19; protocol; policy; longitudinal; coordination; access; impact; virtual care; virtual health; Canada

Introduction

Pre–COVID-19 Challenges in Canadian Primary Care

More than 75% of visits in Canada are within a primary care setting [1]. Access to primary care is the foundation of a strong health care system; it is vital to achieving the quadruple aim of (1) enhancing patient experience, (2) promoting care team well-being, (3) improving population health, and (4) optimizing costs by managing health in primary care through the patient's life course and thereby reducing the burden on acute care [2]. Primary care includes comprehensive and routine care, health promotion, disease prevention, diagnosis and treatment of illness and injury, coordination of care with other specialists, among other care services.

Even prior to the COVID-19 pandemic, Canadians reported lower access to a source of regular primary care than individuals residing in other Commonwealth nations, with only 90% indicating a regular physician and/or place to receive care in 2020 [3]. Access to a regular source of care in Canada, traditionally with family physicians or nurse practitioners, has declined in recent years, and it varies widely across provinces [3,4]. Individuals without a regular primary care provider are classified as "unattached patients" [5,6], and they typically experience poorer health outcomes and less appropriate care than patients with access to a regular primary care provider (ie, attached patients) [7,8]. Vulnerable patients and those with complex needs, including those with low-income levels and/or low social support, are less likely to be attached to a primary care provider, despite the fact that they would benefit more from access to comprehensive and continuous primary care than less vulnerable patients [7,9,10]. Unattached patients are less likely to seek the needed care and more frequently use alternative points of access, such as walk-in clinics, than attached patients [11].

As Canadian provinces struggle to support patient attachment to primary care, specific types of care may be provided by community-based pharmacists in some jurisdictions [12,13]. However, primary care provided by pharmacists may not be sufficient and recommended for all patients, particularly those with chronic or complex health concerns and those with needs outside of pharmacists' legislated scope. Because of these challenges in accessing and *being attached* to a regular primary care provider, many Canadians rely on emergency departments or walk-in clinics to receive care. Among Canadians surveyed in 2020, 42% reported that they had visited an emergency department within the previous 2 years, and among those respondents, 40% indicated their concern could have been treated by a regular primary care provider [3]. Because having access to a regular primary care provider has been shown to reduce the likelihood of emergency department use [14], promoting patient attachment to primary care was a key priority prior to the onset of the COVID-19 pandemic. Most Canadian provinces have therefore developed strategies including centralized waitlists for unattached patients and dedicated clinics to address this concern [15,16].

Early Findings Regarding the Effects of the COVID-19 Pandemic on Primary Care

The COVID-19 pandemic has caused unprecedented disruption to primary care in Canada and internationally. During the peak of the first wave of COVID-19 in Canada, many primary care clinics reduced their work hours [17], leaving patients and caregivers fearful and uncertain about how to access care. Primary care providers were required to make rapid shifts in practice to comply with infection prevention and control requirements, incorporate COVID-19 triage and nonacute case management, address reduced referral and diagnostics access, and implement virtual care where possible [18-21]. Primary care providers also had to engage in practice redesign, secure access to personal protective equipment, and integrate changes in scope of practice in the case of pharmacists in some jurisdictions [22]. Many primary care providers were also redeployed or prepared to be redeployed to COVID-19 testing and treatment roles [21,23].

Health care access is defined as "the opportunity to have health care needs fulfilled" [24]. Access to health care is influenced by (1) the accessibility of providers, organizations, institutions and systems; and (2) the ability of individuals, households, communities, and populations to access primary care. These influential elements have had a COVID-19 "anvil" dropped on their capacity to provide, and access, primary care (see Figure 1).

The COVID-19 pandemic led to delayed and forgone care, concurrent with increased mental health needs of providers and patients. As the pandemic continues, there are anticipated waves of COVID-19 fallout (Figure 2) [25,26]. Although emerging evidence illustrates some significant impacts of the pandemic

on primary care systems globally [17], the effects of the pandemic on patient attachment and access to primary care remain unclear. There is also mounting evidence on the impact of the COVID-19 pandemic on patient and provider well-being [3].

Figure 1. Depiction of the COVID-19–induced disruption to the accessibility of the health care system and the ability of patients to access the system (adapted from Levesque et al [24]).

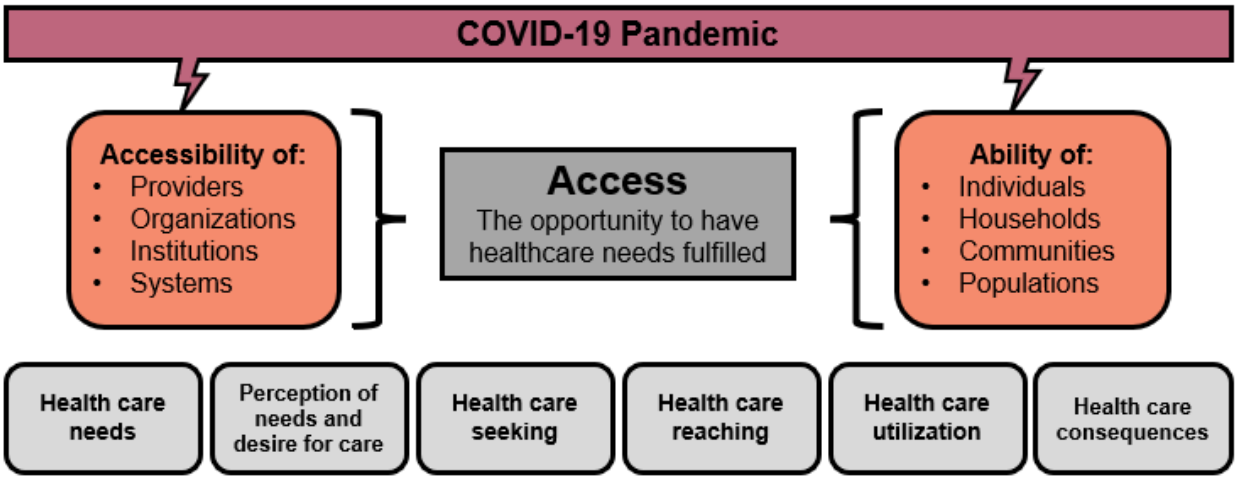
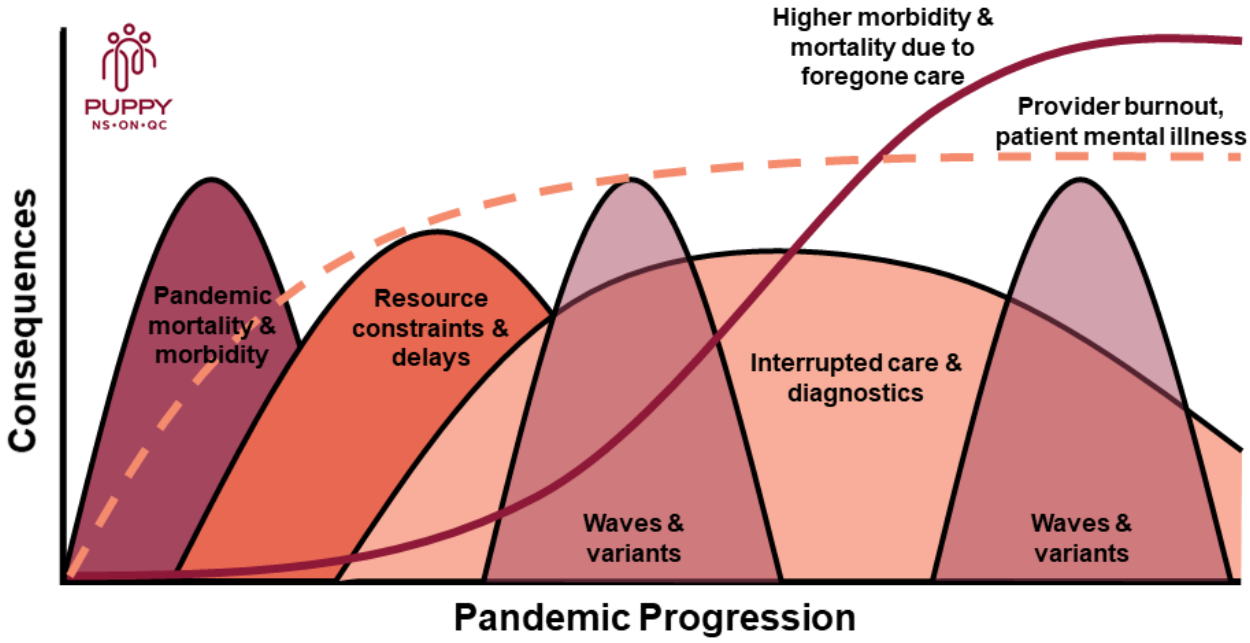


Figure 2. Anticipated waves of the COVID-19 pandemic on primary care.



Pivoting a Program of Primary Care Research to Address the COVID-19 Crisis

At the onset of the COVID-19 pandemic, many health research studies in Canada were required to halt immediately while a pandemic plan and appropriate public health measures were created and enacted. For example, our cross-provincial CUP study (Comparative Analysis of Centralized Waitlist Effectiveness, Policies, and Innovations for Connecting Unattached Patients to Primary Care Providers), funded by the Canadian Institutes of Health Research (CIHR), examining pre–COVID-19 patient attachment to primary care in 3 provinces, namely Ontario (ON), Québec (QC), and Nova Scotia (NS), was put on hold for several months [27].

As the pandemic continued, our team recognized that the existing research aims and methods would not be sufficient to address the effects in the novel COVID-19 context. Furthermore, new research questions were emerging rapidly due to changes in the policy landscape and provider roles in primary care systems across Canada. For these reasons, it was necessary to pivot existing studies to include pandemic-specific analyses and capture changes in primary care systems over time, while identifying novel ways of data collection in a safe manner during the pandemic. Our research team rapidly engaged with our study

team, which included the departments and ministries of health, health authorities, primary care providers and their organizations, and our patient partners. Through these consultations conducted in March and April 2020, we quickly gathered lists of key concerns and priority areas and synthesized and thematically grouped them. The co-principal investigators (EGM, MB, MG, JEI, MM, and BC) then developed new strategies for answering emerging questions and updated the study methods to reflect the new COVID-19 primary health care landscape and ability to work safely. This newly expanded and updated protocol was then submitted for funding in May 2020.

Objectives

This study will identify and evaluate strategies to provide primary care access and COVID-19 triage and care by family physicians, nurse practitioners, and pharmacists that can be scaled-up to promote attachment and improved access for patients across and beyond the COVID-19 waves. We will focus particularly on patients who are unattached, with complex care needs, and/or experiencing social barriers to care, as primary care–based support for these populations may lead to better outcomes for these patients and the health care system across the quadruple aim. Accordingly, the study objectives are as follows:

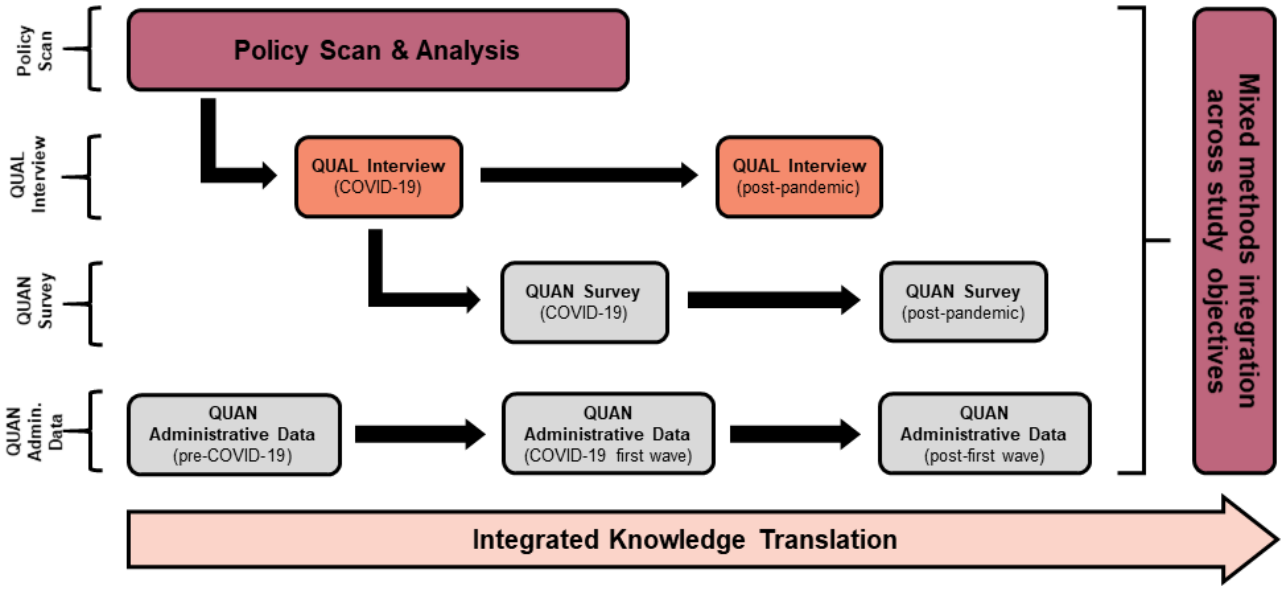
1. To identify primary care policies and interventions implemented in response to the COVID-19 pandemic and to describe how they affect primary care attachment (ie, demand) and accessibility (ie, supply).
2. To understand how COVID-19–related changes affect: (1) patients' experience of accessing primary care, considering different needs, identity factors (eg, age, gender) and access abilities (unattached and attached patients and/or patients with complex needs), and (2) provider health and well-being.
3. To determine how these pandemic-related changes have impacted health care utilization, attachment to primary care providers, and medication prescription, as indicators of access to primary care: We hypothesize that unattached patients and those with chronic conditions are vulnerable to poorer primary care access and health outcomes exacerbated during the COVID-19 pandemic.
4. To share promising strategies to provide access to primary care involving policymakers, primary care providers, and patients across Canada in the immediate, intermediate, and reflective phases of the pandemic.

Methods

Study Design and Setting

To address the rapid effects of the COVID-19 pandemic on policy, practice, and patient access to primary care in line with the objectives described above, a longitudinal mixed-methods observational study building from our team's ongoing research is being conducted. Data will be collected and compared across 3 Canadian provinces (NS, QC, and ON) by using four different methods (see Figure 3) with integration. Data collection will include (1) a content analysis of policies affecting primary care access in the wake of the COVID-19 pandemic; (2) qualitative interviews with providers, patients, and policymakers; (3) surveys of providers and patients; and (4) analysis of administrative data, including centralized waitlists, billing, and prescribing data, to track health care access and utilization, and primary care provider prescribing patterns before, during, and after the COVID-19 pandemic.

Figure 3. Overview of study objectives, methods, and relationships between study activities. QUAL: qualitative analysis; QUAN: quantitative analysis.



Study Participants

A purposeful sampling approach will be applied to include participant representation from key stakeholders in primary care access, including policymakers, patients, and primary care providers via qualitative interviews, surveys, and linked administrative health data (see Table 1). Although providers from many professions contribute to primary care across

systems, our study will focus on family physicians, nurse practitioners, and community pharmacists. The inclusion of the latter is due to the growing number of publicly-funded services offered by pharmacists in several Canadian jurisdictions in recent years, with limited evaluation (eg, prescription for minor ailments, immunizations, reviewing and managing medications) [28-31], which establishes more primary care access options.

Table 1. Participant groups involved in each of the four data collection methods.

Participant group	Data collection method				Knowledge Translation
	Qualitative interviews	Quantitative surveys	Policy content analysis	Administrative data	
Patients	✓	✓		✓	✓
Providers	✓	✓		✓	✓
Policymakers	✓		✓		✓

Policy Content Analysis

Contextual factors affecting primary care access will be identified through extensive provincial policy reviews and interviews with health authority, government, regulator, and corporate policymakers. The unit of analysis considered is provincial. We will document primary care changes in a context that coincides with key developments related to the COVID-19 pandemic to inform recommendations for transformation, scale, and spread. Provincial policies may include provider hiring and funding; delivery models, including the rapid deployment of virtual care modalities across Canada; incentives, programs, and innovations to aid patient access; fulfilling the needs of unattached and other vulnerable patients; and other policies that may play moderating roles in primary care (eg, provider well-being). We will focus on influential policies, where policies are defined by the World Health Organization as “decisions, plans, and actions…undertaken to achieve specific healthcare goals” and identified contextual factors [32].

The Tomoaia-Cotisel approach [33] for assessing and reporting contextual factors of primary care innovations will be applied to the qualitative and policy content analyses components of the study. The framework involves engaging diverse perspectives, considering multiple policy and context levels, time, formal and informal system/culture, and identifying interactions between policies and contexts. It is tailored specifically to innovations in primary care and considers moderators at multiple levels.

Qualitative Interviews

Qualitative methods are designed to elicit experiences and perceptions of phenomena where little is known—an ideal approach to study the impact of the COVID-19 pandemic on primary care. Stakeholder groups to be interviewed include patients, family physicians who do and do not accept new patients, nurse practitioners, community pharmacists, and policymakers with roles relevant to primary care access and attachment. The proposed longitudinal data collection will support interviews, with 10 participants per stakeholder group per province (ie, N=120 participants), which will ensure saturation [34,35].

Interviews will be conducted during and after the COVID-19 pandemic to elicit current and retrospective lived experiences. Interview guides will be developed to reflect key issues pertinent to stakeholders. For example, providers will be asked questions pertaining to changes in their practice. Patients will be asked about their experience with primary care changes and the impact of these changes on access to care and well-being. Policymakers will be invited to share processes for, and outcomes of, policy change and will be consulted on relevant documents to include in our policy content analysis (study objective 1).

Purposive and snowball sampling strategies will be used, with stratification by relevant participant characteristics (gender, rurality, practice characteristics, etc). Invitations for interview participants will be distributed via the provincial centralized waitlists, partnered organizations, and social media. We will iteratively revise our sampling and recruitment strategies as we collect data and learn more about patient and provider experiences [36].

Informed consent discussions and semistructured, in-depth interviews will be conducted virtually using Zoom videoconferencing software (Zoom Video Communications Inc.) by a Masters-trained researcher. Audio recordings of interviews will be transcribed verbatim and coded in NVivo software (QSR International). Coding reports will be generated and examined to uncover themes and patterns in the data.

Preliminary thematic analysis will provide rapid reporting to stakeholders. A framework analysis [37] approach will incorporate the conceptual framework proposed by Levesque et al [24] for access to health care and be implemented across study phases for comparative analysis. This method allows for inductive and deductive coding approaches [37]. We will code deductively using Levesque’s framework and inductively using interview transcripts, thereby allowing emergent themes to enhance what can be gleaned from the framework alone. Intra- and cross-case analysis will be conducted by incorporating provincial framework analysis matrices [37,38].

Quantitative Surveys

Brief surveys for patients and providers will be developed to determine the prevalence of our emerging qualitative themes. Surveys designed for providers will be delivered via the secure web-based Opinio survey tool (Objectplanet, Inc.) in the postpandemic period, to measure the degree to which COVID-19–related policy changes have affected primary care access and attachment, as well as their personal wellness. Recruitment support will be provided by our partners. A web-based patient survey at the same time point will explore patient primary care access and attachment during the

COVID-19 pandemic. A convenience sample of 1000 patient respondents per province (N=3000) will be recruited using a third-party survey sampling company. It is estimated that a sample size of 1000 per province would permit adequate segment sizes for comparison of results among patient groups and provinces. The use of third-party sampling services is common for health care research involving the general public [39]. Bivariable and multiple regression models will be generated to show trends and associations on key elements across phases. Follow-up surveys will be conducted at a later point to assess changes over time.

Administrative Data

Analyses of pre–COVID-19 prescription dispensation, centralized waitlist, physician billing, and inpatient and outpatient hospital discharge data has already begun to examine the effectiveness of centralized waitlists for a related study [27]. As part of the PUPPY study, we will expand this analysis to explore changes across the pre–COVID-19, COVID-19, and postpandemic periods. Harmonized indicators of health care utilization (eg, primary care, emergency, hospitalization, and potentially avoidable inpatient care), primary care attachment indicators (primary care provider attachment and continuity of primary care), and primary care service provision (eg, frequency and type of primary care encounters and continuity of medication dispensation for maintenance of chronic conditions) will be measured across the 3 participating provinces. Change in these indicators, and in care continuity, will be estimated and compared across pandemic wave–indexed study periods.

Multivariable regression will be used to identify potential clinical (eg, patient complexity and comorbidity), demographic, and socioeconomic determinants of primary care need, as well as changes in these indicators over the course of the pandemic. Socioeconomic determinants are derived from the 2016 Canadian census data, including the Canadian Index of Multiple Deprivation, with a focus on dimensions of economic dependency, ethnocultural composition, and situational vulnerability [27]. Centralized waitlist data will be used to measure primary care attachment and assess changes in access to primary care. Building on ongoing work, variation in patient primary care provider attachment rates, demand for attachment, and time to attachment among those patients identified on centralized wait lists will be quantified. Moreover, the changes in these outcomes will be assessed across study periods. Determinants of these outcomes will be identified, and their relative magnitude will be estimated using multivariable techniques. In each province, study populations will be stratified by age, sex (and gender where feasible), degree of comorbidity and geography (ie, urban vs rural) to identify those at greatest risk of being unattached to a primary care provider.

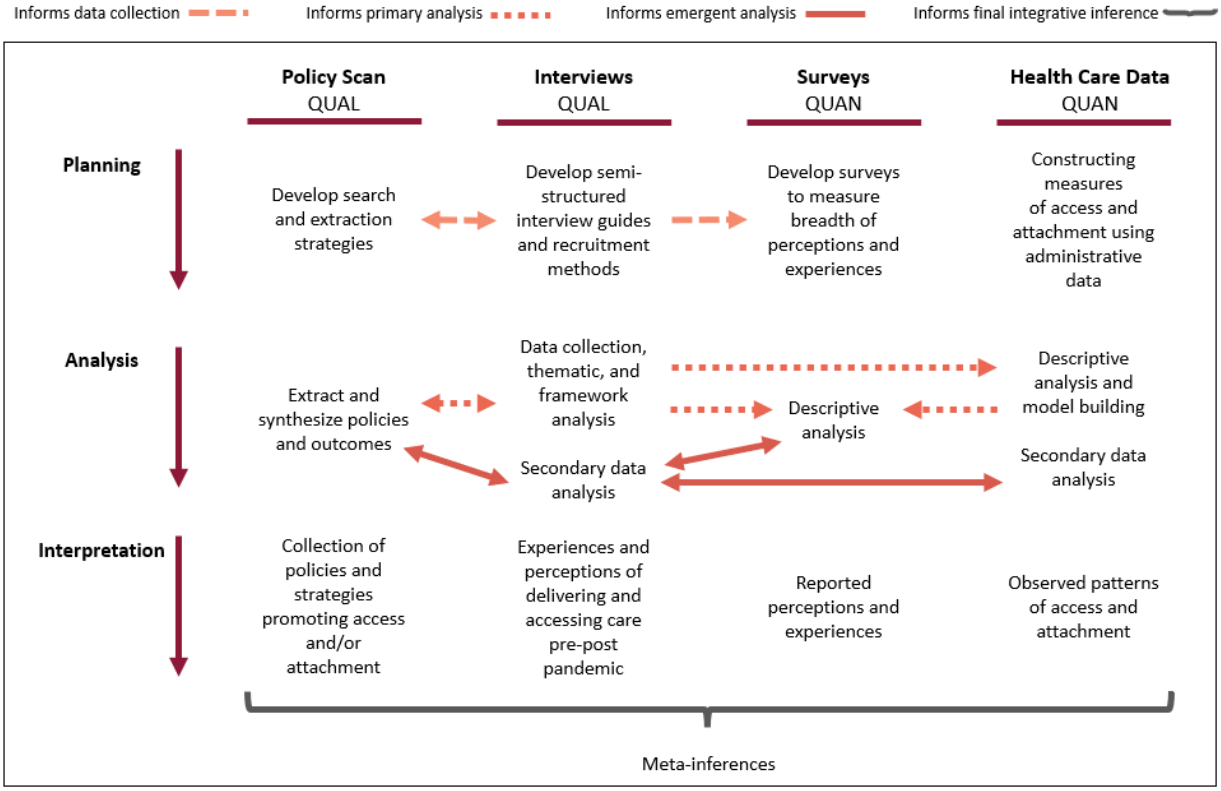
Mixed Methods Integration

As a longitudinal evaluation comparing 3 provincial cases, the study will use a series of mixed methods integration approaches and principles to inform the planning, analysis, and interpretation across the four data types [40]. Adapted from Goldsmith et al [41], Figure 4 provides a depiction of the ways in which the four study methods will inform one another and ultimately lead to meta-inferences strengthened by this mixed methods approach.

In the planning phase, qualitative work and policy content analysis approaches will be conducted in parallel, with findings from each iteratively informing data collection and planning for the other. For example, qualitative interviews will support identification of policy documentation unable to be identified through traditional searches, whereas analysis of policy documents will uncover areas of interest to explore future qualitative interviews. Additionally, in an exploratory sequential approach, qualitative interview findings will be used to inform development of a quantitative survey to build upon and explore the breadth and depth of perceptions expressed by interview participants.

In the analysis phase, data will be collected through embedding and merging—a process by which multiple datasets are collated for analysis and triangulation via iterative comparison [40]. This process will enable creation of rich case descriptions. In particular, a timeline for each case (province) illustrating the patterns in data alongside policy milestones and insight into relevant participant experiences will be developed. The frameworks being used to inform our approaches have been used across multiple methodologies and mixed methods study designs and will facilitate these comparisons [24,33]. As shown in Figure 4, the use of congruent methods will allow numerous comparisons between datasets for both primary and emergent research questions. Mixed methods interpretation will be conducted via the creation of mixed methods narratives and joint displays from which meta-inferences incorporating multiple methodologies can be generated [40].

Figure 4. Summary of mixed methods integration approaches across the planning, analysis, and interpretation stages of the PUPPY study. QUAL: qualitative analysis; QUAN: quantitative analysis.



Results

Funding

In June 2020, our study team received funding through the CIHR COVID-19 Rapid Funding. The funding opportunity encouraged an expansion of ongoing studies to expedite the translation of findings and offered resources to identify and incorporate emerging research questions, expand existing methods, and include additional methods where necessary. Through this opportunity, our team received the resources necessary to undertake this study to elucidate the effects of the COVID-19 pandemic on primary care in Canada. Ethics approval was received in Quebec in December 2020, in Ontario in November 2020, and in Nova Scotia in August 2020.

Ethics

Approval to conduct this study was granted in the Canadian provinces of Ontario (Queens Health Sciences & Affiliated Teaching Hospitals Research Ethics Board, file number 6028052; Western University Health Sciences Research Ethics Board, project 116591; University of Toronto Health Sciences Research Ethics Board, protocol number 40335), Québec (Centre intégré universitaire de santé et de services sociaux de l'Estrie, project number 2020-3446), and Nova Scotia (Nova Scotia Health Research Ethics Board, file number 1024979). As the PUPPY study builds upon and expands the timeline of ongoing research projects, including the CUP study [27], ethical approvals have in several cases been granted as amendments or extensions to the CUP study to facilitate rapid implementation of study activities.

Timeline

Data collection for the PUPPY study will take place in 2021-2022, with rapid reporting between 2021 and 2023. As of April 2021, recruitment for qualitative interviews has begun in NS and QC, with recruitment expected to take place in ON when COVID-19–related constraints have eased. Each province is in the process of accessing administrative health data and linking it to provincial centralized waitlist data. Integrated and end-of-grant knowledge translation of the PUPPY study and subsequent research will follow up on key areas identified.

Discussion

Partnership and Knowledge Translation

Our team includes regulatory bodies and associations representing family physicians, nurse practitioners, and community pharmacists, as well as support from the CIHR's Strategy for Patient Oriented Research (SPOR) Primary and Integrated Healthcare Innovations (PIHCI) Networks and the SPOR Support for Patient-Oriented Research and Trials Units to aid data collection and knowledge dissemination. Guidance from COVID-19 policymaking partners will ensure relevance and uptake while minimizing the burden of study activities on participants, which is particularly critical given the high demands of the pandemic on all stakeholders involved in our study. Data collection activities will occur remotely to comply with public health measures. In anticipation of possible participant distress and recognizing the impact of the pandemic on mental health and wellness generally, we will provide a list

of resources to appropriately trained mental health and primary care providers.

To ensure appropriate dissemination and translation of study findings, all data collection begins with consultation. Team members representing all stakeholder groups, including providers, policymakers, and patients, will participate in the development and refinement of study tools, analysis, interpretation, and dissemination plans. Knowledge dissemination will include multiple modalities to maximize the uptake of findings. Policy briefs and reports will be shared at each study phase and will be assisted by professional graphic and communication design support. Other modalities include peer-reviewed publications, conference presentations, local presentations to key stakeholder groups (eg, provider associations, health authorities, departments or ministries of health, and primary care provincial leadership meetings), knowledge sharing on departmental websites, blog posts, and social media. Team members, including patient partners, will have the opportunity to inform, author, and participate in dissemination activities. Using CUP study funds in the post-pandemic period, we will facilitate cross-jurisdictional learning via a symposium with stakeholders from across Canada to improve primary care attachment and to manage patients within and outside of pandemics.

Conclusions

The PUPPY study is designed to provide rapid support for primary care policymaking, provider needs, and patient access to primary care based on the investigation across the various COVID-19 waves. We will regularly communicate emerging recommendations to our partners for timely policy optimization. Immediate-term early data collection will provide feedback on new policies in primary care settings and effects on patient access, thereby providing insight into possible unintended consequences of rapid policy transformation and revealing promising strategies. This information will inform provision of care through changing pandemic contexts, including requirements for physical distancing and safety requirements. In the intermediate term, our study will document changes in the primary care policy landscape to strengthen the response to additional “waves” related to COVID-19 outbreaks. Findings will be distributed to study partners and beyond via our networks (eg, CanCOVID, pan-Canadian PIHCI Networks, and North American Primary Care Research Group), to support cross-jurisdictional pandemic response. In the long term, the study findings will help us grasp the impact of these policy changes and events on the ability of systems and providers to coordinate and deliver primary care, patient access to primary care, and on health outcomes. Recommended best practices to improve access to primary care as we transition to a post-pandemic context will be widely shared with our partners via our knowledge dissemination plan as outlined above.

Acknowledgments

We would like to acknowledge the generous support of the organizational partners and team members, including the academic researchers, providers, policymakers, and patient partners (Sarah Peddle, Ana Correa Woodrow, Nicole Desjardins, and Danièle Roberge). A full list of our team members and partners can be found on the study website [42]. We would like to thank the Canadian Institutes of Health Research for their support in the form of a COVID-19 Rapid Funding Opportunity Grant (grant 447605).

Authors' Contributions

The study was conceived by the lead author (EGM) who also led the writing of the manuscript with active assistance from the coauthors. All authors made substantive contributions to the conception and design of the study, which includes qualitative, quantitative, mixed methods, patient engagement, and knowledge translation components. All authors have critically reviewed this manuscript and approve the version to be published.

Conflicts of Interest

None declared.

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Abbreviations

CIHR: Canadian Institutes of Health Research
CUP: Comparative analysis of centralized waitlist effectiveness, policies, and innovations for connecting unattached patients to primary care providers
PIHCI: Primary and Integrated Healthcare Innovations
PUPPY: Problems Coordinating and Accessing Primary Care for Attached and Unattached Patients Exacerbated During the COVID-19 Pandemic Year
SPOR: Strategy for Patient Oriented Research

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Protocol

Female Genital Mutilation/Cutting Education for Midwives and Nurses as Informed by Women's Experiences: Protocol for an Exploratory Sequential Mixed Methods Study

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Abstract

Background: Female genital mutilation/cutting (FGM/C) is a complex and deeply rooted sociocultural custom that is innately entrenched in the lives of those who continue its practice despite the physical and psychological dangers it perpetrates. FGM/C is considered a significant independent risk factor for adverse maternal and fetal outcomes in pregnancy and childbirth. Several studies in high-income countries have explored the experiences and needs of women with FGM/C as well as the knowledge of the health professionals, particularly midwives and nurses, who care for them. However, to date, no studies have evaluated the implementation of education for health professionals in high-income countries to meet the specific needs of women with FGM/C.

Objective: This study aims to explore the impact of an FGM/C education program for midwives and nurses as informed by the experiences of women with FGM/C accessing maternity, gynecological, and sexual health services in South Australia.

Methods: This study will adopt a three-phase, exploratory sequential mixed methods design. Phase 1 will involve the *exploration* of women with FGM/C views and experiences accessing maternity and gynecological (including sexual health) services in South Australia. The findings from phase 1 will inform phase 2: the *development* of an educational program for midwives and nurses on the health and cultural needs of women with FGM/C. Phase 3 will involve the *evaluation* of the program by measuring midwives' and nurses' changes in knowledge, attitude, and practice immediately before and after the education as well as 4 months after completing the program. Phase 1 of this study has been approved by the Women's and Children's Health Network human research ethics committee (ID number 2021/HRE00156) and the University of South Australia human research ethics committee (ID number 204096).

Results: Phase 1 will commence in August 2021, with the interpretation of findings being undertaken by November 2021. Phase 2 will be developed and facilitated by February 2022, and the final phase of this study will begin in March 2022. This study is expected to be completed by February 2023.

Conclusions: The findings of this research will provide insight into the development and evaluation of education programs for midwives and nurses that includes collaboration with women from culturally and linguistically diverse backgrounds to address the specific cultural and health needs of communities.

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KEYWORDS

education; midwives; nurses; female genital mutilation/cutting; maternity care; women's health care, knowledge; attitude; practice

Introduction

Background

The Australian Institute of Health and Welfare estimates that 53,000 girls and women living in Australia have undergone female genital mutilation/cutting (FGM/C) [1]. However, it is not clear how many girls and women are at risk of being illegally subjected to the practice as there are no formal guidelines, policies, or training for health professionals on the identification, reporting, and management of FGM/C cases in Australia [2]. In 2014, a report by Family Planning New South Wales found that the mandatory collection and reporting of FGM/C cases could only be achieved through adequate education and training of health professionals on FGM/C [3].

Girls and women with FGM/C can experience serious immediate and long-term health complications because of the practice [4]. Childbirth can be a particularly challenging time for women with FGM/C, as the physical and psychological complications of FGM/C may be exacerbated [5-10]. Furthermore, FGM/C is considered a significant independent risk factor for adverse maternal and fetal outcomes in pregnancy and childbirth [11]. Despite this, midwives and nurses often report that they are not equipped to effectively support women with FGM/C because of a lack of educational opportunities [12,13]. Some midwives and nurses report that they do not have the knowledge, clinical skills, cultural competence, confidence, and awareness of legal responsibilities to effectively support the needs of women with FGM/C, elements that are essential in the provision of woman-centered care [14].

Research on the effectiveness of FGM/C focuses on prevention programs; however, it has demonstrated that the key to success is through engagement and collaboration with women and affected communities [2,15,16]. With regard to exploring the experiences of women with FGM/C to assist in the design of education for midwives and nurses, there appears to be a gap in the literature. Therefore, this study protocol will engage and listen to women with FGM/C to assist in the development of an education program for health professionals (ie, midwives and nurses who work in maternity, sexual, and reproductive health services) and to improve midwives' and nurses' clinical skills, cultural competence, confidence, and awareness of legal responsibilities to effectively support the needs of women with FGM/C. This paper describes a study protocol for the development and evaluation of an educational module on FGM/C for midwives and nurses as informed by women's experiences.

Aims

This study aims to explore the views and experiences of women with FGM/C accessing maternity, gynecological, and sexual health services in South Australia to assist in the development of an educational program for midwives and nurses.

Objectives

The objectives of this study are as follows:

- To design an FGM/C education module for midwives and nurses in collaboration with women who have experienced FGM/C to meet their cultural and health needs.
- To collaborate with key stakeholders to assist with the development of an FGM/C education and training program for midwives and nurses.
- To evaluate the impact of the FGM/C education and training program and assess the knowledge, attitudes, and practice (KAP) of midwives and nurses providing care to women with FGM/C.

Research Questions

The research questions are as follows:

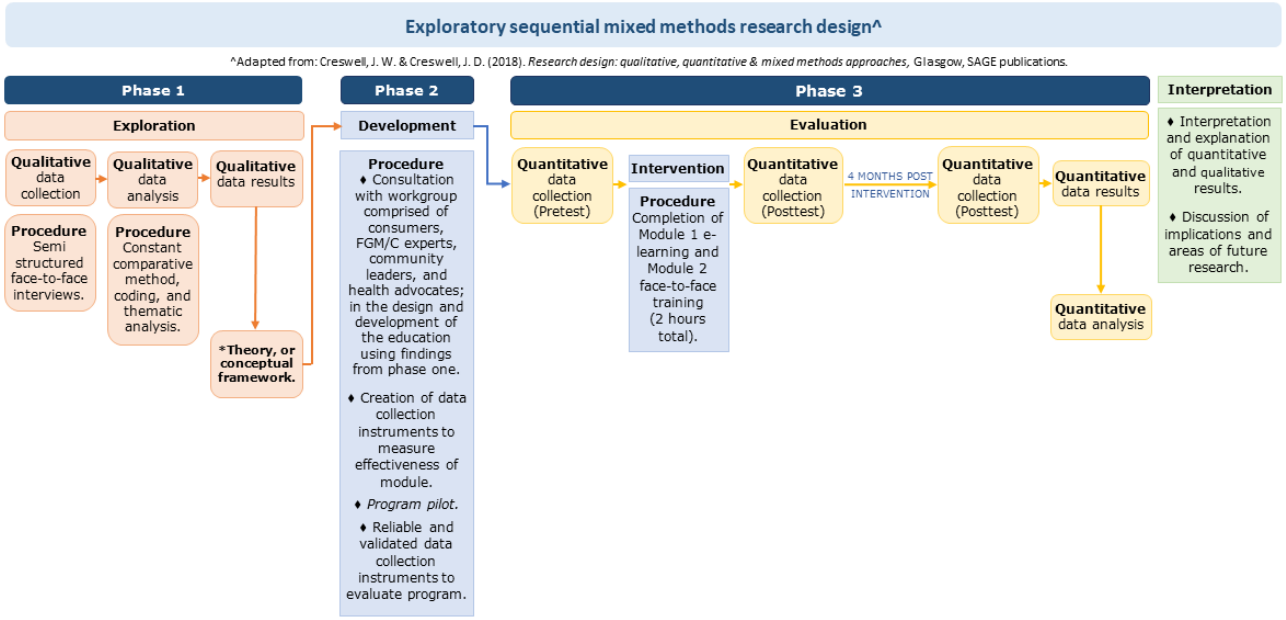
1. What are the views and experiences of women with FGM/C in South Australia?
2. What factors affect the experiences of women with FGM/C accessing maternity, gynecological, and sexual health services in South Australia?
3. What FGM/C education and training resources are currently available and accessible to midwives and nurses in Australia?
4. What impact does FGM/C education and training have on the knowledge, attitude, and clinical practice of midwives and nurses when supporting women with FGM/C?

Methods

Study Design

This proposed study will use a three-phase, exploratory, sequential mixed methods design (Figure 1). Phase 1 will be *exploration* of the views and experiences of women with FGM/C accessing maternity, gynecological, and sexual health services in South Australia. The findings from phase 1 will be used to inform phase 2: *development* facilitation of an FGM/C educational and training program for midwives and nurses. Phase 3 will involve the *evaluation* of the education and training program and measure the KAP of midwives and nurses before and after completing the course.

Figure 1. Exploratory sequential mixed methods research design [17]. FGM/C: female genital mutilation/cutting.



Conceptual Framework

A mixed methods research design is a systematic way of *combining or integrating* qualitative and quantitative methods, data collection, and analysis to thoroughly examine a concept or issue that a single construct may not be able to capture completely [17,18]. This approach is pragmatic and enables researchers to be *open* to using a range of research methods, assumptions, and worldviews to attain a deeper understanding of the phenomenon under investigation [17]. Integrating qualitative and quantitative data in mixed methods allows each approach to complement each other, in turn, strengthening the findings and decreasing the weakness of using a single construct [17].

This proposed study will adopt an exploratory, sequential mixed methods design as the most suitable construct to answer the proposed research questions. Exploratory designs are data driven and enable researchers to *explore* the topic first where there is limited understanding of it or no prior conceptual frameworks [17].

Setting

This research will be undertaken in metropolitan and regional South Australia. Participants will be sought from public, private, and community health sectors that provide maternity, gynecological, and sexual health care services.

Sampling

A purposeful nonprobability sampling technique will be used to recruit participants for this study [19,20]. The aim of a purposive sample is to describe a group of participants with the same or similar characteristics (eg, women with FGM/C who have accessed health services in South Australia and registered midwives and nurses practicing in South Australia) [21].

Participants

This study will recruit 2 different cohorts of participants for phases 1 and 3 of the study.

Phase 1 Participants

This includes women living in South Australia who self-identify as having FGM/C (types 1-4).

Inclusion Criteria

The criteria for inclusion are as follows: (1) women aged >18 years; (2) identify as having FGM/C (type 1-4); (3) reside in South Australia; and (4) have accessed maternity, gynecological, and sexual health services in South Australia in the past 5 years.

Exclusion Criteria

The criteria for exclusion are as follows: (1) women aged <18 years; (2) have not experienced FGM/C; (3) do not reside in South Australia; (4) have not accessed maternity, gynecological, and sexual health services in South Australia; and (5) are unable to provide informed consent. Please note that the ability of women to speak or understand the English language will not be a requirement in this research, as qualified interpreters will be used. Interpreters with experience in translating in health care settings from South Australian Health–approved interpreting services will be used in this study.

Phase 3 Participants

This includes midwives and nurses registered with the Australian Health Practitioner Regulation Agency.

Inclusion Criteria

The criteria for inclusion are as follows: (1) registered midwives and nurses, (2) working in clinical practice in South Australia, and (3) have cared for or will care for women with FGM/C.

Exclusion Criteria

The criteria for exclusion are as follows: (1) not a registered midwife or nurse, and (2) not working in clinical practice in South Australia.

Recruitment

Recruitment for each phase will occur in 3 stages.

Stage One

In phase 1, participants will be recruited through the study's website and the principal researcher. Advertisements and study website information will be placed on social media, and posters will be displayed at several clinical sites across South Australia. Information sessions will be provided to midwives and nurses in clinical settings to increase awareness of the study and how to advise potential participants to access the study's website and contact information of the principal researcher. Women will be able to express their interest in the study by emailing or phoning the principal researcher directly or by registering their interest through the study's website. The principal researcher will contact the women to discuss the study, answer any questions, and inform them of what is required to participate in the study.

Stage Two

In phase 2, participants will be women (from phase 1) and professionals who have expertise in supporting women who have experienced FGM/C, community leaders, and health advocates. The FGM/C experts, community leaders, and health advocates will be recruited through snowball sampling and via email, inviting them to be part of the collaboration group.

Stage Three

Phase 3 will be the recruitment of registered midwives and nurses currently practicing in South Australia, working in maternity, gynecology, and sexual health services. Participants will be invited to participate in phase 3, that is, the *evaluation* of an education and training program through advertisements on social media, the Australian College of Midwives, the Australian Nursing and Midwifery Federation, South Australia Health information sessions, and the University of South Australia (UniSA).

Ethical Considerations

This project has ethical approval from the Women's and Children's Health Network human research ethics committee (ID number 2021/HRE00156) and the UniSA human research ethics committee (ID number 204096).

Consent

Participants in phase 1 will be provided with a participant information sheet (PIS) to read in plain English or translated to Arabic, Swahili, Somali, Tigrinya, Amharic, Indonesian, and Malay languages (common languages spoken by FGM/C-practicing communities [22]). The PIS will explain the details of the study, including the purpose of the research, participation requirements, confidentiality, data management, consent process, and how the research information collected will be used. Participants will have access to the PIS in a digital format on the study's website or a hard copy in the form of a pamphlet.

For women who are unable to read English, an audio recording of the written information of the PIS and consent form will be available in their preferred language, and/or an interpreter will be available to read the forms to the women. At this stage, the women will be informed of the researchers' intention to use their contact details to invite them to participate in a working group for phase 2 of the study.

Participants in phase 3 (midwives and nurses) will also be provided with a PIS specific to phase 3. The PIS will have detailed information regarding the purpose of the research, participation requirements, confidentiality, data management, consent process, and how the research information collected will be used. All participants (from phases 1 and 3) will be required to provide written consent before commencing the study, with a copy provided to them for their records.

Participant Safety and Withdrawal

Participation in the study will be voluntary. Participants can withdraw from the study at any time before the interviews take place and before the deidentification of transcript verbatim (phase 1) as well as before commencing the education program (phase 3). Any data collected up to the point of withdrawal will be included in the final data analysis. No additional data will be collected after withdrawal. Withdrawing from the study will not affect the woman's access to health services.

Cultural Considerations

Owing to the sensitive and emotive nature of FGM/C, there are several potential cultural issues that are anticipated by the researchers, and measures will be put in place to minimize the effect, as outlined in the sections below.

Reluctance to Speak About FGM/C

FGM/C is considered a taboo women's issue and a topic that women are not willing to openly discuss. Feelings of shame and stigma associated with the criminalization of FGM/C in high-income countries may make women reluctant to disclose information surrounding the issue out of fear of discrimination or legal repercussions. Several studies have demonstrated that community support is the single most important aspect in establishing a strong rapport with women with FGM/C [16,23,24]. Therefore, to minimize these concerns, the researchers will liaise with community leaders, FGM/C clinical experts, and health advocates to gain their support and guidance to develop a framework on how to best support women participating in the study. Community leaders and FGM/C experts will also review the information and language used in the recruitment posters, postcards, PIS, and the study's website.

Vulnerable Women, Domestic Violence, and Reliving Psychological Trauma

Overview

FGM/C is recognized as a violation of the human rights of girls and women globally [22]. The practice is a deeply embedded sociocultural tradition among practicing communities, posing many challenges to its eradication, as women can be both the victims and perpetrators of FGM/C [15]. Women with FGM/C are more likely to experience sexual intimate partner violence than women who have not had the procedure [25,26]. It is well documented that storytelling triggers several concerns for victims of abuse, particularly, reliving the psychological trauma and resurfacing of suppressed memories [7,27]. Anticipating these issues, the researchers will take steps to address these and minimize any distress for participants.

The following steps will be followed during recruitment

- Researchers will ensure that all potential participants will have a complete understanding of their rights to withdraw from the study without any consequences.
- Confidentiality will be maintained, and the benefits and risks of the study, privacy, and respect of women's cultural values as detailed in the PIS and consent forms provided will be explained.
- In phase 1 recruitment stage, the researchers will ensure that women considering participating in the study understand that the research team is only interested in their experience in accessing health services in South Australia and not the events that led to FGM/C. However, if women wish to discuss their personal experiences, they will be supported during the interview to do so.
- Participants wishing to discuss any aspects of the study or concerns will be able to do so at any time by contacting the principal researcher directly (phone numbers and emails will be supplied).
- Full disclosure of researchers' duty of care to ensure participants' safety, including mandatory reporting under the *South Australian Criminal Law Consolidation Act 1935* and the *Children's Protection Act 1993*, will be explained.
- The following steps will be followed while the study is being conducted: At the beginning of phases 1 and 3, the researchers will reiterate the information given to participants during recruitment and provide an opportunity for further questions.
- A safe, private environment (either at the UniSA City East campus or at a place where the woman feels most comfortable and of her choosing) will be used to undertake the interviews in phase 1.
- Participants who become distressed at any time of the study will be provided with an opportunity to take a break from the interview and only recommence if they wish to continue. A *participant support protocol pathway* (Multimedia Appendix 1) will be used to ensure that women are provided all the necessary support.
- Any intimate partner violence concerns identified during the study will be addressed by offering the participant support and referral information to specialized services (eg, Women's Safety Services South Australia: migrant women support, Domestic Violence Gateway Service, National Sexual Assault Domestic Family Violence Counselling Service, Relationships Australia, South Australia Police and Specialized Family Violence Service, Survivors of Torture and Trauma Assistance and Rehabilitation Service, and Refugee Health Service).

After the Study

Participants will be provided with an opportunity to discuss any concerns at the end of their participation.

Confidentiality

The participants' confidentiality will be maintained through a deidentified collection of data. In phase 1, interview transcripts will be given pseudonyms to separate the data but no identifiable characteristics will be collected to maintain confidentiality. All possible identifiable characteristics (names of people or places) in the transcripts will be omitted to prevent inadvertent deductive disclosure. In phase 3, the program evaluation questionnaires will be deidentified at the point of collection. Participants will be emailed a randomly assigned log-in code to access the education program. The code will be used by the participant for the duration of the study and will not be linked back to the participant. No identifiable characteristics will be used in the reporting of qualitative findings and quantitative results.

Data Management Plan

Participants' confidentiality will be maintained through the deidentified collection of data. Interview recordings will be collected with a handheld voice recorder and erased after transcription. Questionnaires will be deidentified at the point of collection to prevent participants from being identified. The data management process will be organized according to the UniSA guidelines and using My Data Management Plan tool (a UniSA program).

Storage archiving of data will be stored on the web via software provided by the UniSA local server. Data files will be stored in at least 2 locations to reduce complete loss. Data will be stored on a USB drive and a PC (password protected) at UniSA. Data will be frequently backed up on the UniSA server. Data will remain confidential and limit access only to the research team. Hard copy data collection tools will be stored in a locked filing cabinet in a locked room at the UniSA City East campus. Measures will be taken to ensure the security of information from misuse, loss, or unauthorized access while stored during the research project. Research data and records will be maintained for 5 years after publication. This storage of data requirement complies with the ownership and retention of data policy, as outlined by the National Statement on Ethical Conduct in Human Research and UniSA data storage policy.

In terms of secure data destruction, the primary investigator will obtain written approval from the executive dean of the UniSA Clinical and Health Sciences Unit for secure destruction of research data, materials, and associated research records. This data material will be shredded and disposed of in confidential, secure document destruction bins provided at the university. All data stored electronically will be deleted through a process of repeated overwriting of the documents and deletion from the server, ensuring that the contents cannot be recovered.

Procedure

Phase 1: Exploration

Interviews (Option 1)

Women will have the choice of attending an interview in person at UniSA City East campus or via telephone at a prearranged date and time.

Semistructured interviews will be used to explore the views and experiences of women with FGM/C who have accessed or are currently accessing maternity, gynecological, and/or sexual health services in South Australia for this phase. Semistructured questions will be asked by the researcher using examples identified from previous studies that have investigated the views and experiences of women with FGM/C [16,28]. The questions will be asked in a flexible manner and adapted, omitted, or

elaborated on to correspond to the individual needs of each participant.

At the end of the interview, the principal researcher will provide participants with an opportunity to check and confirm responses and that these are a true representation of their views and experiences. If there is anything women would like to clarify or omit, they can do so. No further changes will be possible once data analysis or publication is conducted.

Data Saturation

Data saturation will be attained when no new themes are identified [29,30]. Data saturation will be guided by the Hennink et al [30] framework. These researchers reported that data saturation could be achieved with 10 interviews but recommended that researchers should conduct a further 3 interviews to ensure that no new themes arise.

Web-Based Survey (Option 2)

The investigators acknowledge that some women will not want to reveal that they have had FGM/C but may still want to share their views and experiences accessing maternity, gynecological, and sexual health services. Women who wish to remain anonymous will have the option to complete a web-based questionnaire on the study's webpage. The web-based questions will be the same semistructured questions used in the face-to-face interviews. Women will be able to review their answers before submission.

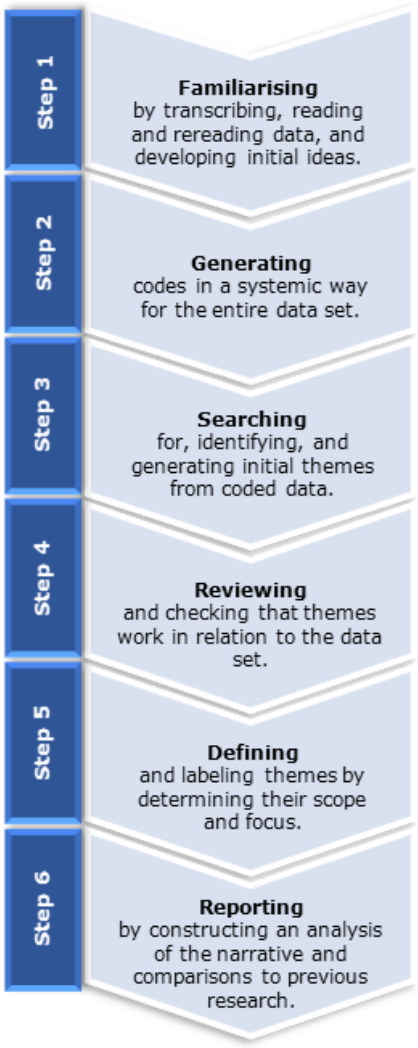
Data Analysis

The interview data will be manually transcribed by the principal researcher using the manual transcription function on the NVivo 12 (QRS International) software within 24-48 hours. No data will be saved on the cloud function of the program. A second researcher will check the accuracy of the scripts transcribed verbatim.

Constant comparative method (CCM) will be used to analyze data and generate codes from themes [31,32]. CCM uses a systematic process for analyzing interviews by constantly comparing the data, from "incident to incident, concepts emerging from further incidents in new data, and concept to concept" [32] to generate a theory. This approach enables researchers to identify gaps that require more exploration in future interviews. CCM has been used extensively in grounded theory research and can also be used effectively within other qualitative research [31,32].

Themes will be generated using the 6 steps for reflexive thematic analysis by Braun and Clarke [33] (Figure 2). Any discrepancies or disagreements will be resolved through open discussions with the research team.

Figure 2. Braun and Clarke's [33] reflexive thematic analysis.



Gratuity

Women in the face-to-face and telephone interviews will be given an Aus $50 (US $37) gift card to reimburse their time and travel or parking costs.

Phase 2: Development

Overview

A workgroup collaborative will be established to develop the education and training program. The group will consist of women with FGM/C, health advocates, community leaders, and FGM/C clinical experts. The findings from phase 1 will inform the content of the program. The education program will be divided into 2 modules: module 1 (e-learning) and module 2 (face-to-face training).

Module 1: e-Learning

Module 1, an e-learning module, will cover the theoretical aspects of FGM/C, including, but not limited to the following:

1. Understanding FGM/C, including background and types of FGM/C
2. Understanding the law
3. Physical and psychosexual implications of FGM/C
4. Management of complications arising from FGM/C
5. Communicating with women living with FGM/C
6. Deinfibulation
7. Caring for women across the childbirth continuum
8. Additional resources

Module 2: Face-to-Face Training

Module 2 will be a 1-hour face-to-face interactive training session delivered at various clinical sites around South Australia. The session will provide participants with a summary of the information learned in module 1, a chance to discuss questions and any aspects of the course further, and an opportunity to consolidate their understanding of the theory. Phase 1 will inform the development of case studies that review the health needs and care of women with FGM/C in the antenatal, intrapartum, and postpartum periods based on the experiences of women. The training will involve group work and will be facilitated by the principal researcher. The content will include conducting sensitive history taking, effective documentation, use of interpreters, deinfibulation counseling, and physical examinations.

Data Collection Tools

KAP changes among midwives and nurses will be measured using 3 questionnaires: (1) a multiple-choice questionnaire to measure knowledge, (2) a 5-point-Likert scale survey to measure attitude, and (3) a survey to measure practice. The questionnaires will be developed based on previously validated questions identified in the literature that have evaluated FGM/C education for health professionals [34]. Knowledge will be measured via a multiple-choice questionnaire designed from the content of the program. Multiple-choice questionnaires are a convenient and effective assessment tool that has been extensively used in research to test knowledge [35-38].

Midwives' and nurses' attitudes toward FGM/C will be measured using 5-point Likert scales, adapted from 3 previous studies that have evaluated the implementation of education and training on FGM/C for health professionals [36,39,40]. Participants will be given a series of statements from which they will be required to select the extent to which they agree or disagree with each (ie, strongly agree, agree, neutral, disagree, and strongly disagree).

Information on the experience (practice) of midwives and nurses caring and supporting women with FGM/C will be collected through a survey that covers midwives' and nurses' experiences with FGM/C history taking, physical examinations, reinfibulation, mandatory reporting, and care plans.

Participants' demographics, such as age, qualifications, years of clinical practice, and area of expertise, will be collected only once via a survey that will be completed on the web before commencing module 1.

Content Validity

Content validity of the FGM/C education program and data collection tools will be conducted by an expert panel of clinicians, FGM/C experts, and nursing and midwifery academics. Feedback will be sought on the content, wording, and structure of the education program and questionnaires and instructions to participants. Any disagreements among the members of the expert panel will be addressed through discussion and changes to the content until a consensus is reached [41].

Test-Retest Reliability

Test-retest reliability will be used to measure the reliability of the validated questionnaire [42]. Midwife or nurse volunteers will be invited to complete the questionnaires at the same time and then 2 weeks later. Correlations between the scores at both time points will be measured, and the instruments will be determined to be reliable or not. Reliability refers to the consistency of the tool that measures the same trait in the same person and situation at different points in time [42]. Instruments that are reliable guarantee the accuracy and replicability of the results in future studies by reducing random error and bias [43].

Pilot of Module 1

The education program (including questionnaires) will be piloted with a sample of 10 midwives and nurses who will not be involved in the study. These participants will be asked to complete an evaluation form to inform the researchers if any changes need to be made. The information that will be sought includes the relevance of the module to practice, navigation of the module, ease of access to the content, relevance of questionnaires, and time it took to complete.

Sample Size

Owing to the lack of previous data on the effect of FGM/C education on practicing midwives' and nurses' knowledge and attitudes, sample size calculation was conducted to detect a standardized medium effect (d=0.5). Reflective of the pre- and posttest design, a paired sample size calculation was conducted using the SAS/STAT version 14.2 software at a significance level of 0.05 and power of 0.9. Using a two-sided test and allowing for 20% loss to follow-up, a sample size of 55 nurses or midwives will be required to complete phase 3.

Phase 3: Evaluation

Midwives or nurses who consent to participate in the study will be provided a log-in to the web-based module using a personal code and password that will be emailed to them before the commencement of the study. Instructions on how to navigate the module and complete the assessments will be provided at the start of the program. Participants will be asked to complete a demographic questionnaire to gather information about their characteristics before commencing the module. Participants will then complete the 3 KAP questionnaires (pretest). Each question must be answered before the next one is provided to reduce nonresponse bias [44]. Access to the content of the module will only occur once the questionnaires are completed and submitted. The results will not be provided to avoid participants remembering their answers for the follow-up questionnaire posttest. At the completion of module 1, participants will be prompted to repeat the knowledge and attitude questionnaires only (posttest). Participants will be encouraged to complete the module and questionnaires on the same day to avoid any changes to the domains being tested, which could be caused by other types of learning outside of the intervention.

After 4 weeks of completion of module 1, all participants will receive an email with instructions for enrolling in module 2 (in-person training). Various dates, times, and venues will be provided during the consent stage to maximize attendance of module 2. Participants who attend the sessions will be asked to complete all 3 KAP questionnaires one more time at the beginning of the training day. The questionnaires will be paper based because of convenience, and it is less expensive than providing computer access to all the participants. This should reduce the attrition commonly observed in longitudinal studies [45,46]. At the end of the workshop, participants will be provided with a certificate of completion and 2 hours of continuing professional development points.

Phase 3 data will be analyzed using the SAS/STAT 14.2. Descriptive statistical analysis will be used to describe participants' baseline characteristics. Continuous variables will be described using means and SDs. Categorical variables will be presented as frequencies and proportions. A paired sample two-tailed *t* test will be used to analyze the differences in knowledge and attitudes before and after the workshop, respectively. McNemar test compares the binomial proportions in a paired sample. It will be used in the study to test the changes in practice before and after the workshop.

Results

The sequential exploratory design nature of this study will help researchers develop an educational module for midwives and nurses that is inclusive of the cultural and health needs of women with FGM/C. The data-driven nature of the exploratory mixed methods design allows the exploration of the topic where there is currently limited evidence—in this case, the experiences and health needs of women with FGM/C accessing maternity, gynecological, and sexual health services in South Australia.

This study will begin with an exploration of the topic in phase 1 to hear from women with FGM/C. This will be undertaken through face-to-face interviews and/or web-based questionnaires (open-ended questions) that will gather qualitative data. The findings will be analyzed and used to inform the development of an FGM/C bespoke education program for midwives and nurses as a way of *connecting* the data in phase 2 [17]. The education program will then be evaluated using pre- and posttest questionnaires to produce quantitative data in phase 3. This process is known as sequential, where one phase of the mixed methods informs or *builds* on the next [18].

Discussion

Importance of This Research

Notwithstanding worldwide campaigns to put an end to FGM/C, its prevalence continues because of a combination of cultural, religious, and social factors [22]. The World Health Organization estimates that 200 million girls and women have had FGM/C, and another 3 million are at risk every year [22]. Girls and women with FGM/C can suffer from serious short-and long-term complications, including physical, sexual, and psychological issues because of this practice [47]. FGM/C is considered an independent risk factor for adverse maternal and fetal outcomes in pregnancy and childbirth, resulting in a substantial financial impact on health services [48]. Women with types 1 and 2 of FGM/C are 3 and 5 times, respectively, more likely to sustain severe perineal trauma (third and fourth degree tears) than women who have not had the procedure [47].

In 2013, the Australian government made a commitment to end FGM/C by funding community awareness and education, reviewing Australia's legal framework, and encouraging research and data collection to obtain the necessary evidence to support women and girls with FGM/C in Australia [49]. However, the implementation of these strategies has been slow to reach communities, and the practice continues. A total of 4 people have recently been convicted in Australia, in 2 separate cases, for performing FGM/C on a child and taking another overseas for the procedure [50,51]. These convictions highlight the need for more education and research in Australia and the mandatory reporting of FGM/C cases.

The most recent National Strategic Directions for Australian Maternity Services aims to ensure that maternity services in Australia are "equitable, safe, woman-centred, informed, and evidence-based" [52]. As such, women of culturally and linguistically diverse backgrounds need to have access to services that are responsive to their cultural needs, including access to interpreters, culturally trained health professionals, and bilingual and bicultural health advocates. The report informs the need to have routine antenatal identification of women with FGM/C and associated risk factors. This research will contribute to improving health services for women with FGM/C and provide evidence to inform health policies.

Phase 1 of this study is expected to be completed by November 2021. Phase 2 will commence from December 2021, with the aim of undertaking phase 3 in February 2022.

Conclusions

As far as the authors are aware, there are no other studies that have used the views and experiences of women with FGM/C, or demonstrated a collaboration with relevant stakeholders, to develop an education program to educate midwives and nurses on the cultural and health needs of women from culturally and linguistically diverse backgrounds.

The findings and results from this exploratory mixed methods study will be collated, and meta-inferences will be developed and discussed. This research will be disseminated via publications and conference papers. The project outcomes will inform the provision of woman-centered health care education for midwives and nurses in South Australia.

Acknowledgments

This project is funded by an Australian Government Research Training Program domestic stipend and has a completion date of February 2023.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Support protocol for face-to-face interviews.
[PDF File (Adobe PDF File), 213 KB - resprot_v10i10e32911_app1.pdf]

Multimedia Appendix 2
Peer-review report (reviewer 1) by University of South Australia.
[PDF File (Adobe PDF File), 141 KB - resprot_v10i10e32911_app2.pdf]

Multimedia Appendix 3
Peer-review report (reviewer 2) by University of South Australia.
[PDF File (Adobe PDF File), 171 KB - resprot_v10i10e32911_app3.pdf]

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Abbreviations

CCM: constant comparative method
FGM/C: female genital mutilation/cutting
KAP: knowledge, attitude, and practice
PIS: participant information sheet
UniSA: University of South Australia

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Protocol

Pharmacokinetics and Perceptions of Children and Young Adults Using Cannabis for Attention-Deficit/Hyperactivity Disorder and Oppositional Defiant Disorder: Protocol for a Mixed Methods Proof-of-Concept Study

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Abstract

Background: Despite the lack of evidence on the use of cannabis for the treatment of attention-deficit/hyperactivity disorder (ADHD), the growing perception that cannabis is safe has led more patients and caregivers to self-medicate. Some psychiatrists now authorize medicinal cannabis for patients with ADHD with features of oppositional defiant disorder (ODD) to curtail the unregulated (ie, self-medicated) use of recreational cannabis or to offer a therapeutic option to those who continue to experience symptoms after exhausting all other treatment options.

Objective: This protocol aims to explore the perceived effectiveness and pharmacokinetics of cannabis in youth and young adults, who are currently taking it as part of their treatment plan for ADHD with features of ODD, under the supervision of a psychiatrist.

Methods: Patients between the ages of 12 and 25 years with a diagnosis of ADHD and features of ODD, who are currently taking cannabis herbal extract (at a Δ^9-tetrahydrocannabinol [THC]:cannabidiol [CBD] ratio of 1:20) as a treatment adjunct to stimulant pharmacotherapy will be recruited. A sample size of 10-20 individuals is estimated. The study interview will consist of (1) validated symptom rating scales (Swanson, Nolan, and Pelham-IV Questionnaire [SNAP-IV], 90-item; Patient Health Questionnaire, 9-item [PHQ-9]; and Screen for Child Anxiety Related Emotional Disorders [SCARED] tool to measure symptoms of ADHD and ODD, depression, and anxiety, respectively); (2) a semistructured interview to probe the experiences of using cannabis; and (3) a cannabis side effects survey. A cannabis product sample as well as 2 blood samples (a trough level and 2-hour postdose level) will be collected to measure plasma concentrations of cannabinoids and relevant metabolites (THC, CBD, 11-hydroxy-THC, 7-hydroxy-CBD, cannabichromene, and 11-nor-9-carboxy-THB) using liquid chromatography–tandem mass spectrometry (LC–MS/MS). Self-report rating scales (SNAP-IV, SCARED, and PHQ-9) will be scored in accordance with standard protocols and compared to retrospective scores obtained from the participant's chart. Demographic variables (age, weight, and race), symptom scores, and blood levels (peaks and troughs) of THC, CBD, cannabichromene (CBC), and metabolites will be summarized using descriptive statistics. Relationships between plasma concentrations and symptom scores will be determined using analysis of variance, and multiple regression analysis will be performed to determine associations between plasma concentrations and demographic variables (age, weight, and ethnicity). The qualitative data will be audio-recorded and transcribed and organized into themes.

Results: The protocol was approved by the Biomedical Research Ethics Board at the University of Saskatchewan (protocol #1726), and recruitment began in May 2021.

Conclusions: This proof-of-concept study will explore the potential treatment effectiveness of medical cannabis in participants with ADHD and ODD through a mixed methods approach to inform future research in this area.

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KEYWORDS

attention-deficit/hyperactivity disorder; ADHD; oppositional defiant disorder; cannabis; cannabidiol; young adults; youths; pharmacokinetics; marijuana

Introduction

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental health conditions in children, with an estimated worldwide prevalence of 7.2% [1]. This chronic neurobehavioral disorder is characterized by inattention and hyperactivity-impulsivity and affects both children and teens, with up to 60% of those affected exhibiting symptoms into adulthood [2]. Treatment of ADHD typically involves nonpharmacologic strategies (eg, healthy diet, education, and cognitive and behavioral interventions), and pharmacologic therapy with a psychostimulant (eg, methylphenidate) [3]. While stimulant pharmacotherapy is effective for treating the core symptoms of ADHD, in approximately 70%-90% of cases, symptoms of aggression are less likely to respond. Approximately 35%-65% of children with ADHD exhibit comorbid disruptive behavior disorders (DBDs; oppositional defiant disorder [ODD], or conduct disorder) [4,5], and a substantial number continue to exhibit aggressive and disruptive behaviors even after stimulant treatment [4-6]. The consequences of inadequately treated aggressive and disruptive behaviors are significant; these children are more likely to have encounters with the justice system, deficits in academic achievement, behavioral and disciplinary problems, and substance use challenges [7].

Cannabis Use and ADHD

The growing perception that cannabis may be useful for alleviating ADHD symptoms has motivated individuals to use cannabis without the necessary evidence to support its use and without clear guidance on appropriate dosing [8,9]. A recent study of internet-based discussions about the effects of cannabis on ADHD found at least 3 times as many comments advocating for cannabis' therapeutic benefits, compared to comments regarding harm or lack of efficacy [10]. Moreover, several parents of children with ADHD have admitted to administering cannabis to their children for symptom management [8,11].

Some adults with ADHD have reported benefits from using cannabis. These benefits include feeling calmer, improved sleep, and the ability to sustain focus [12]. Patients with ADHD typically use cannabis "to improve their mood and sleep" rather than "to get high" [13]. Cannabinoids act on the endocannabinoid system, which is a signaling system consisting of 2 receptor subtypes (CB1 and CB2). ADHD involves a dysregulation of dopamine, and stimulant pharmacotherapy works by blocking the reuptake of dopamine as a result of the inhibition of noradrenergic areas in the prefrontal cortex [14]. CB1 receptors also interact with the dopaminergic system, and it is hypothesized that the modulation of endocannabinoids in the medial prefrontal cortex and the ventral tegmental area may lead to regulation of the impulsive action and restraint [15,16]. Several other neurotransmitters, such as glutamate, γ-aminobutyric acid, and *N*-methyl-D-aspartate, as well as CB2 receptors can interact with endocannabinoids and may contribute to the modulation of impulsivity [15-17].

Co-occurring substance use is one of the most common problems associated with ADHD. Children with ADHD are at an increased risk for both using cannabis and having a cannabis use disorder, and these youth are nearly 3 times more likely to report cannabis later in life compared to the general population [10,18]. Whether or not potential harms associated with substance use are worse for youth with ADHD is currently unknown.

The self-medication theory is one possible theory to explain the increased risk of substance misuse in some patients [19,20]. This hypothesis, which is a theory about addiction, originally focused on why and how individuals were drawn to heroin and cocaine [19]. In 1997, it was updated to consider a variety of other applications [20]. Based on decades of clinical observation, it proposes that patients consume drugs in an effort to cope with the illness or treatment side effects [19,20]. In the case of ADHD, individuals may self-medicate to alleviate negative emotionality, such as anger, sadness, anxiety, and inadequate emotional regulation [21]. In medicine, the decision to initiate a medication or other treatment is based on the theoretical gains in therapeutic benefits weighed against the potential harms [22]. Observational studies indicate that cannabis may improve symptom management and decrease side effects associated with prescription medication, or as a substitute for alcohol and illicit drugs [16,23,24]. Nonmedical cannabis use has also helped to decrease cocaine dependence in a study of patients with ADHD [25]. In this capacity, cannabis substitution could be considered a harm reduction strategy [22]. Some psychiatrists within our institution have now resorted to prescribing medicinal cannabis for patients with ADHD and ODD who were using unregulated cannabis recreationally, or "self-medicating," or among those who continue to experience symptoms after exhausting all other treatment options. The dearth of evidence regarding cannabis use for ADHD bespeaks an urgent need to determine whether cannabis use is safe and effective in these individuals.

Goal of the Study

The goal of this pilot study is to examine the real-world effectiveness by comparing changes in their disease-related symptoms before and after beginning treatment with medical cannabis, using validated assessment scales for ADHD, ODD, depression, and anxiety. We will characterize their experiences with using medical cannabis by way of a semistructured interview and cannabis side effects survey. Furthermore, blood levels of commonly found cannabinoids in cannabis in children and young adults who are currently taking medical cannabis for the treatment of their ADHD and ODD under the care of a pediatric psychiatrist will be correlated with symptom scores and demographic variables (age, weight, and ethnicity). Finally, a sample of the participant's cannabis will be analyzed through liquid chromatography–tandem mass spectrometry (LC–MS/MS) to confirm its chemical composition.

Specific Objectives and Hypotheses

Hypothesis 1: Patients who use medicinal cannabis perceive improvements in ADHD and ODD symptoms.

Hypothesis 2: Improvements in self-reported symptom scores associate with higher plasma levels of cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) and their bioactive metabolites.

Primary Objectives

1. Examine the changes between self-report ADHD scores (as measured by the symptom scores of the Swanson, Nolan, and Pelham-IV Questionnaire [SNAP-IV, 90-item]) before (retrospectively) and after the initiation of medical cannabis.
2. Examine potential associations between steady-state plasma concentrations of CBD, THC, cannabichromene (CBC), and well-known metabolites in children with symptom scores of the SNAP-IV (90-item).
3. Characterize the experiences of participants using medical cannabis.

Secondary Objective

1. Examine potential associations between self-reported symptom scores from other validated ADHD assessment tools (Screen for Child Anxiety Related Emotional Disorders [SCARED] rating scale, and Patient Health Questionnaire, 9-item [PHQ-9]), and steady-state plasma concentrations of CBD, THC, CBC, and well-known metabolites in children using cannabis for ADHD with ODD.

Methods

Study Design and Inclusion Criteria

An observational, mixed methods, proof-of-concept study will be undertaken at 1 center in Saskatchewan. The protocol was designed to minimize face-to-face contact, so the study can be performed during the COVID-19 pandemic. Patients with ADHD and ODD who are currently taking cannabis herbal extract (at a THC:CBD ratio of 1:20) as a treatment adjunct to stimulant pharmacotherapy are eligible to participate. Participants are between the ages of 12 and 25 years; have a diagnosis of ADHD in accordance with Diagnostic and Statistical Manual of Mental Disorders (5th edition) with features of ODD; are stabilized on medical cannabis herbal extract (at a THC:CBD ratio of 1:20); and have been deemed safe to participate by the study physician. Participants under the age of 18 years must also have the permission of a guardian to participate. We acknowledge that some patients with ADHD may have comorbid mental health disorders, such as autism spectrum disorder. For the purpose of this study, though, we will only enroll participants who are functionally able and willing to provide assent. We will aim to enroll at between 10 and 20 participants in this pilot study.

Enrollment and Consent

Potential participants and their caregivers will be identified and initially contacted by the study physician (DQ) through his childhood and adolescent psychiatry practice at the Saskatchewan Health Authority (SHA) in Saskatoon (Saskatchewan, Canada). If the family is interested in learning more, their contact information will be forwarded to a research team member who will follow up with the family. Potential participants (and guardians, if applicable) who express interest will be provided with a copy of the consent form and the study information reviewed. If the participant (and caregiver, if applicable) opts to participate, logistics will be arranged and informed consent taken.

Study Interview

Overview

A study interview will be performed at a mutually convenient time for the participant (and caregiver, if applicable) and research team member. The interviews are expected to last approximately 40-60 minutes each and will be conducted via Cisco WebEx or phone, depending on the participant's preference. If the participant requires a break during the interview, we will accommodate this need. The interviews will be audio-taped, and notes recorded by the researcher, but all information gathered from the participant will be kept confidential. Demographic information is collected, including cannabis product and dosing regimen, age, sex, clinical diagnosis, ethnicity, other medications, and participants' self-reported height and weight. Self-reported rating scales are used to measure participants' current symptoms of ADHD and debility, and a semistructured interview will be used to explore their experiences of cannabis use.

Self-reported Symptom Rating Scales

The SNAP-IV (90-item) is a revision of the original SNAP questionnaire [26,27], which contains items from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria to assess inattention (items 1-9), hyperactivity/impulsivity (items 11-19), and ODD (items 21-28). Items have also been added to summarize the Inattention, Hyperactivity/Impulsivity, and ODD domains (items 10, 20, 29, and 30), as well as items representing a general index of childhood problems (items 31-90). Each item measures the frequency or severity of a symptom or behavior, on a Likert scale of 0-3 (0=not at all and 3=very much). This instrument has been shown to have good reliability and validity in different study samples [28].

The PHQ-9 is a 9-item tool used for screening, diagnosing, monitoring, and measuring the severity of depression [29] (Multimedia Appendix 1). Each item is scored on a Likert scale of 0-3 (0=not at all and 3=nearly every day). The items are summed to equal a total between 0 and 27, with higher scores equating to a higher level of debility [29].

The SCARED tool, which assesses anxiety symptoms, consists of 41 items and 5 factors that parallel the DSM-IV classification of anxiety disorders [30]. Each item is scored on a Likert scale of 0-2 (0=not true or hardly ever true and 2=very true or often true). A score of ≥25 may indicate the presence of an anxiety disorder and scores higher than 30 are increasingly specific [30].

Cannabis Use Questions

A semistructured interview guide will be used to characterize the perceptions of participants (and guardians, if applicable) of cannabis treatment. The interview guide was drafted a priori by the research team and was piloted on 3 patients who use cannabis therapeutically. The interview consists of 6 open-ended questions, which explore participant's life circumstances before initiating medical cannabis, contributing factors for choosing this treatment, how (if at all) things have changed, what concerns (if any) might exist about treatment, and how the participant obtains the medical cannabis (Multimedia Appendix 2). The interviews will be flexible, depending on the participant's responses and probes will be used to delve further into potential areas of interest. No time restrictions will be placed on the interview. Rather, the conversation continues until data saturation is reached, and no further information is offered from the participant. Field notes will be taken throughout the interview to capture nuances of the conversation. Finally, a cannabis side effect survey [31] will be administered, which capture potential side effects experienced from taking cannabis within the previous week. Potential side effects in this survey are categorized under the domains of cognitive, physiological, psychological, movement, and artistic/social, and response choices for each item include "yes," "no," or "uncertain."

Blood Collection

Within 1 week of the interview, the mobile laboratory will visit the participant's residence to obtain 2 blood samples for evaluation of the plasma levels of CBD, THC, CBC, and active metabolites. Measured metabolites will include 11-hydroxy-Δ^9-THC (11-OH-THC) and 7-OH-cannabidiol. A trough level (immediately before the morning cannabis dose) will be collected to represent the minimum steady-state plasma drug concentration ($C_{SS,min}$), while a 2-hour postdose level is collected to represent the maximum steady-state plasma drug concentration ($C_{ss,max}$; where therapeutic effect should be the highest) [32,33]. Blood samples (1 mL each) will be collected into BD Vacutainer Barricor tubes [34] and centrifuged at 2000 × g for 5 minutes to separate plasma. Samples will be subsequently transferred to Eppendorf Protein LoBind microcentrifuge tubes and transported on ice, until they reach the laboratory for storage in a –80°C freezer.

Concurrent medications will be continued by the participant as per usual. No dietary restrictions are imposed on the day of the pharmacokinetic analysis, to capture the real-world situation of patients using cannabis herbal extract as an adjunct treatment to stimulant therapy.

Cannabis Sample Collection

Participants are provided with an option to have a small sample (<0.5 mL) of their cannabidiol oil collected on the day of the blood collection, to be analyzed in the laboratory. The purpose is to confirm the composition of the cannabis product. The results of this analysis will be communicated back to the participant.

Data Analysis

Sample Size Determination and Power Calculation

Since there is an absence of literature in this area, with this proof-of-concept study, we aim to recruit as many subjects as possible up to a maximum of 20 participants. The data obtained from this pilot analysis will be used to inform future clinical studies.

Cannabis Analysis

The medical cannabis product sample will be analyzed for the major cannabinoids in the product (eg, THC, CBD, and CBC). The plasma concentrations obtained from the participant will undergo analysis for the major cannabinoids and their relevant metabolites (THC, CBD, 11-OH-THC, 7-OH-CBD, CBC, and 11-nor-9-carboxy-THC (THC-COOH) using LC–MS/MS. This method has been previously developed and validated within our institution [35] in accordance with the guidelines of the Food and Drug Administration [36].

Quantitative Analysis

The self-reported rating scales (SNAP-IV, SCARED, and PHQ-9) will be scored in accordance with standard guidelines. Changes in rating scores will be determined by subtracting the baseline score (obtained prior to cannabis initiation) available in the participant's medical chart, from the final score obtained during the interview. Demographic variables (age, weight, and racial background), symptoms scores, and blood levels (peaks and troughs) of THC, CBD, CBC, and metabolites will be summarized using descriptive statistics. Adverse effects will be summarized descriptively or listed. Differences between plasma concentrations and symptom scores will be determined using analysis of variance (ANOVA) and multiple regression analysis will be used to determine associations between plasma concentrations and demographic variables (age, weight, and racial background). Spearman ρ will be used to calculate correlation coefficients. To control for the increased type I error resulting from these multiple comparisons, the level of significance will be set to $P \leq .01$. Statistical analyses will be performed using SPSS (version 27, IBM Corp).

Qualitative Analysis

Audiotapes from the interviews will be transcribed verbatim and the data will be input into NVivo qualitative software. The data will be coded by one of the study investigators and will be reviewed by one of the primary investigators. Discrepancies between the investigators will be resolved through discussion and debate and the second primary investigator will weigh in

if needed. The data will be organized into common themes and summarized.

Results

The protocol was approved by the Biomedical Research Ethics Boards at the University of Saskatchewan (protocol #1726). Recruitment began in May 2021.

Discussion

Principal Findings

Legalization of recreational cannabis occurred in Canada in October 2018. The increased public accessibility, coupled with perceptions that cannabis is "natural" and perhaps "safer" than some of the other available pharmacotherapeutic agents [8,9], has increased the probability of cannabis use in this population, despite an absence of evidence on efficacy or safety in youth or young adults.

At the time this study was designed, only 1 controlled clinical trial was published on the use of cannabis in ADHD. Cooper et al [37] performed a (pilot) randomized controlled trial using Sativex Oromucosal Spray (1:1 THC:CBD) or placebo, in 30 adults with ADHD. Participants in the Sativex group demonstrated a pattern of improved cognitive performance as measured by the QbTest, nominally significant improvements in symptoms of hyperactivity/impulsivity (P=.03), and trends toward improvement for inattention and emotional lability. All trends were strengthened when the per-protocol analysis was performed [37]. Case reports have also described the beneficial effects of cannabis on ADHD symptoms [16,38].

Controlled clinical trials are clearly needed to determine the impact of cannabis use on ADHD symptoms in youth and young adults. Understanding the impact of pharmacotherapy is of particular importance in the pediatric population, where development may be adversely and unpredictably impacted by drug therapy [39]. However, pilot studies need to precede interventional studies to understand feasibility and to glean important information about the pharmacokinetics of cannabis in the pediatric patient population to guide dosing strategies.

While the small sample size of this pilot study will preclude treatment recommendations, the importance of this study should not be understated. Exploring the real-world effectiveness and pharmacokinetics of cannabis in a cohort that is already taking cannabis is the most ethical way to gather the necessary information for initiating a research program in this area. If the results from this pilot study are positive, our future work will include a single dose pharmacokinetic study and eventually a randomized controlled trial.

Conclusions

Novel treatment strategies are needed for patients who experience symptoms of ADHD and ODD despite stimulant pharmacotherapy. Some desperate families have resorted to using cannabis, despite the lack of safety or efficacy data. This pilot study will be the first to explore the real-world effectiveness, perceptions, and pharmacokinetics of cannabis in children and young adults, and the results will guide future study in this area.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Questions from the Patient Health Questionnaire, 9-item (PHQ-9).
[DOCX File , 17 KB - resprot_v10i10e31281_app1.docx]

Multimedia Appendix 2
Semistructured Interview Guide.
[DOCX File , 16 KB - resprot_v10i10e31281_app2.docx]

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Abbreviations

11-OH-THC: 11-hydroxy-Δ9-tetrahydrocannabinol
ADHD: attention-deficit/hyperactivity disorder
CBC: cannabichromene
CBD: cannabidiol
$C_{ss,max}$: maximum steady-state plasma drug concentration
$C_{ss,min}$: minimum steady-state plasma drug concentration
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders
LC–MS/MS: liquid chromatography–tandem mass spectrometry
ODD: oppositional defiant disorder
PHQ-9: Patient Health Questionnaire, 9-item
SCARED: Screen for Child Anxiety Related Emotional Disorders
SHA: Saskatchewan Health Authority
SNAP-IV: Swanson, Nolan, and Pelham-IV Questionnaire
THC: Δ9-tetrahydrocannabinol
THC-COOH: 11-nor-9-carboxy-tertrahydrocannabinol

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Protocol

Efficacy of Cladribine Tablets as a Treatment for People With Multiple Sclerosis: Protocol for the CLOBAS Study (Cladribine, a Multicenter, Long-term Efficacy and Biomarker Australian Study)

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Abstract

Background: Cladribine tablets (marketed as Mavenclad) are a new oral therapy, which has recently been listed on the pharmaceutical benefits scheme in Australia for the treatment of relapsing multiple sclerosis (MS). The current dosing schedule is for 2 courses given a year apart, which has been shown to be effective for treatment of MS for up to 4 years in 75% of patients (based on annualized relapse rate). However, the reinitiation of therapy after year 4 has not been studied.

Objective: This study aims to evaluate the safety and efficacy of cladribine tablets over a 6-year period, according to no evidence of disease activity 3.

Methods: This will be a multicenter, 6-year, phase IV, low interventional, observational study that incorporates clinical, hematological, biochemical, epigenetic, radiological and cognitive biomarkers of disease. Participants considered for treatment with cladribine as part of their routine clinical care will be consented to take part in the study. They will be monitored at regular

intervals during the initial course of medication administration in years 1 and 2. After year 3, patients will have the option of redosing, if clinically indicated, or to switch to another disease-modifying therapy. Throughout the duration of the study, we will assess blood-based biomarkers including lymphocyte subsets, serum neurofilament light chain, DNA methylation, and RNA analysis as well as magnetic resonance imaging findings (brain volume and/or lesion load) and cognitive performance.

Results: This study has been approved by the Hunter New England Local Health District Human Research Ethics Committee. Recruitment began in March of 2019 and was completed by June 2021.

Conclusions: This will be the first long-term efficacy trial of cladribine, which offers reinitiation of therapy in the 3rd year, based on disease activity, after the initial 2 courses. We expect that this study will indicate whether any of the assessed biomarkers can be used to predict treatment efficacy or the need for future reinitiation of cladribine in people with MS.

Trial Registration: This study is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000257167) with Universal Trial Number (U1111-1228-2165).

International Registered Report Identifier (IRRID): DERR1-10.2196/24969

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KEYWORDS

multiple sclerosis; cladribine; biomarkers

Introduction

Overview

Multiple sclerosis (MS) is a common, immune-mediated, demyelinating disease that affects the central nervous system. MS has a highly variable course; therefore, patient-specific treatment decisions are becoming increasingly important. Currently, we have no way to differentiate between the patients who will acquire rapid disability progression and the ones who will remain stable over several years. Most studies point toward early intervention giving a better long-term outcome; however, long-term immunosuppression is associated with increased adverse risk [1,2]. Generally, MS therapies are long-term and some have a demonstrated rebound phenomenon precluding them from being stopped for long periods of time, such as fingolimod [3] and natalizumab [4]. However, there are currently 2 drugs that can potentially be used for immune reconstitution treatment: alemtuzumab and cladribine.

Alemtuzumab is administered in 2 courses, via infusion, 1 year apart. In the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis Study (CARE-MS) extension trial, a redosing scheme was introduced, with up to 4 additional doses being offered in the event of recurring clinical activity [5]. Cladribine is a synthetic purine analog, and its mechanism of action is thought to be primarily via induction of apoptosis in lymphocytes [6]. It was shown in a phase III trial (A Safety and Efficacy Study of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis; CLARITY) to be highly effective in controlling disease activity [7-10]. With a no evidence of disease activity 3 (NEDA 3) rate of 44% over 2 years [7], it is placed in the range of the most efficacious disease-modifying therapies (DMTs) along with alemtuzumab (39%) [11,12] and ocrelizumab (47%) [13]. Furthermore, after 2 years of treatment and 2 years of follow-up (treatment free), 75% of patients with MS remained relapse free [8,14]. However, clinical stability beyond year 4, and additional doses of cladribine tablets based on clinical activity, has not yet been studied.

In the study discussed below, we will offer additional doses of cladribine tablets after 3 years. We aim to compare the clinical outcomes of patients with MS who received additional doses of cladribine with those who changed DMT. We also aim to identify biomarkers for disease control that can be used for treatment decisions, such as redosing with cladribine tablets versus change of DMT.

Justification of Outcome Measures: NEDA

With the introduction of an ever-increasing number of DMTs, our treatment goals have shifted from simply reducing relapses to achieving *NEDA*.

In MS, NEDA 3 is defined as no clinically confirmed progression, no relapse, and no new or enlarging or gadolinium (Gd)-enhancing lesions [15]. This has since been expanded to NEDA 4, which includes brain atrophy [16]. Although our current treatments are increasingly effective, only 30% of patients with MS reach NEDA 4 after 2 years [17]. The rate of NEDA 4 in patients with MS treated with cladribine has not yet been established.

Magnetic Resonance Imaging for Assessing Progression of MS

Magnetic resonance imaging (MRI) has been established as the most reliable indicator of long-term outcomes. Sormani et al [18] analyzed data from 13 large clinical trials, including 13,500 patients with MS, to show that new T2 lesions can predict disability progression. This prediction was significantly improved when combined with brain atrophy [18]. Some of the high efficacy treatments can change the rate of brain volume loss to that seen in the normal aging population [19]. As MRI technology advances, it has become clear that some substructures such as thalamic volume, lateral ventricle, and gray or white matter volume might be even more sensitive and correlate better with clinical outcomes [20].

Lymphocytes as Biomarkers

Blood-based biomarkers are attractive because of their ease of collection and cost-effectiveness. In addition, they may better reflect or even predict disease activity. Lymphocyte subsets

may be good markers of disease stability, as many currently used therapies act by restoring the balance of immune cells in the periphery to a *healthy* state. Therapies affecting the B-cell population have been described as effective treatments for MS [21]. This may be related to the suppression of memory B cells. This theory is supported by the failure of Atacicept and tumor necrosis factor α inhibitors in treating MS, both of which result in disease activation [21]. In both ORACLE-MS and CLARITY, cladribine has been shown to markedly reduce B cells, while having a more modest reduction in T cells and natural killer cells [22,23]. A more recent study of the CLARITY cohort further characterized this reduction and demonstrated that memory B cells were the predominantly affected subtype [24].

These studies investigated lymphocyte subsets over the course of 1-2 years. Therefore, a long-term investigation of lymphocyte subsets in response to cladribine treatment is warranted.

Cognitive Dysfunction in MS

Cognitive impairment is a prevalent symptom in MS, with rates of approximately 40%-70% [25]. The severity of cognitive deficits varies, but unlike the physical symptoms associated with MS, cognitive deficits are unlikely to remit and are associated with a higher risk of progression [26-28]. A recent systematic review evaluated the literature on cognitive impairment and employment status and found a consensus that patients with MS who are unemployed or have reduced work hours record weaker cognitive scores [29]. Loss of employment is a major concern for patients with MS, particularly as the disease is often diagnosed in people of working age, who are just establishing careers and families. Despite this, cognitive testing is often disregarded in terms of clinical trial outcomes. Several tools have been developed to evaluate cognitive function, including the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) [30]. The BICAMS is quick and easy to administer and has recently been validated in the Australian population [31].

Global Epigenetic Profiles in MS

Epigenetics is a rapidly developing area of medical research and refers to the potentially reversible regulation of genomic functions, particularly gene expression. This provides a mechanism whereby an organism can dynamically respond to a change in its environment (eg, DMTs) and alter its gene expression accordingly. DNA methylation is a well-characterized, relatively easy to study epigenetic modification and generally refers to the addition of a methyl group to a cytosine base, followed by a guanidine (referred to as a CpG dinucleotide).

We, and others, have described differential DNA methylation profiles between healthy controls and patients with MS, as well as between relapsing remitting MS and secondary progressive MS [32-38]. In addition, we and others have performed longitudinal studies that found epigenetic profiles are altered after dimethyl fumarate treatment [39-41], making it a potentially specific biomarker for treatment response.

Neurofilaments are a Promising Biomarker

Neurofilament (NfL) light chains are found in neuronal cells but are shed into the cerebrospinal fluid upon neuronal damage and are detectable in the peripheral blood. Increased serum NfL levels have been identified in patients with MS compared with that in healthy controls [42]. These levels show a strong correlation not only with cerebrospinal fluid NfL levels but also with the presence and activity of focal lesions and clinical outcomes [42]. This makes them a promising biomarker not only of disease activity but also disease progression. These may be useful indicators of the need for additional courses of treatment.

Objective

The primary objective of the study is to evaluate the safety and efficacy of cladribine tablets over a 6-year period according to NEDA 3. We will also evaluate clinical outcomes and cognition over a 6-year period, blood-based and MRI-based biomarkers for their ability to predict treatment response, disease activity, and the need to redose cladribine subsequent to the 2-year, 2 initial courses.

Methods

Study Design

This study is a multicenter, 6-year, phase IV, low interventional trial. Enrollment of 150 patients with MS was planned across 9 specialist MS clinics in Australia. The Therapeutic Goods Australia approved a cumulative dose of cladribine (10 mg) tablets as 3.5 mg/kg body weight over 2 years administered as 1 treatment course of 1.75 mg/kg per year. After 3 years, patients with MS in consultation with their health care provider will discuss the option of redosing with cladribine tablets, if clinically indicated (by relapse or new MRI activity), switch to another DMT, or continue without change (without commencement of any DMT). For those who will be continued on cladribine, additional courses will be administered as per the previous dosing of 1.75 mg/kg per year.

Eligibility Criteria

Patients must meet the criteria as described below (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participants must be eligible for and already intend to commence cladribine tablets in accordance with the Australian Product Information (PI). Cladribine tablets are indicated for relapsing remitting patients with multiple sclerosis who do not have HIV infection, active chronic infection, are immunocompromised, have severe renal impairment, or are pregnant or breastfeeding.
- Participants must have the ability to understand the purpose and risks of the study, as outlined in the patient informed consent form and provide signed and informed consent and authorization to use protected health information in accordance with national and local privacy regulations.
- The participants must meet the McDonald criteria [43] for the diagnosis of relapsing remitting multiple sclerosis.
- Male or female participants aged 18-70 years.
- Be able to provide details for or consent to provide access to a stored minimum data set (ie, demographics, date of diagnosis, relapse information, and baseline expanded disability status scale score).
- Be able and willing to comply with all study procedures, including magnetic resonance imaging scanning, as per the protocol.
- Must agree to use contraception from baseline until 6 months after the last dose of cladribine tablets, unless they or their partners are infertile or surgically sterile.
- Participants must be aware of all precautions listed in the PI for Mavenclad, and any subsequent disease-modifying therapy treatment received within this clinical study must be adhered to.

Exclusion criteria

- Participants must not have a concurrent diagnosis of neurological, psychiatric, or other diseases that, in the opinion of the investigator, could impair the capacity to provide informed consent, interfere with study assessments, or impair the participant's ability to comply with the study protocol.
- Any contraindication to magnetic resonance imaging scanning.
- Participants who have any contraindications listed on the Australian PI or who have any of the listed precautions listed on the Australian PI.
- The subject is considered by the investigator, for any reason, to be an unsuitable candidate for the trial.

Assessments

NEDA Status

NEDA-3 and NEDA-4 status (absence of clinical relapses, confirmed disability worsening, and new T2 lesions, including brain atrophy [NEDA-4 only]) will be assessed based on the clinical data uploaded into the database (MSBase) [44]. For this study, we will use the NEDA-4 criteria as defined by Kappos [16]. Physical examinations, vital sign assessments, and expanded disability status scale (EDSS) assessments will be performed throughout the study. Concomitant medications and adverse events are assessed at every study visit. On the basis of clinical and MRI parameters, patients with MS will be classified as NEDA-positive (responders) or NEDA-negative (nonresponders).

MRI Analysis

3D volumetric sequences will be performed annually in routine clinical practice and before treatment switch. The sequence will be performed on the same 3 tesla MRI scanner with a consistent protocol and without gadolinium administration. The images will be transmitted to the Sydney Neuroimaging Analysis Centre for volumetric analysis.

BICAMS Test

Cognition will be measured using BICAMS [30]. This test consists of the oral Symbol Digit Modalities Test (SDMT), the immediate word recall trials of the California Verbal Learning Test-2, and the Brief Visuospatial Memory Test Revised [30]. We chose the BICAMS as a cognitive tool over other available cognitive tests because of its ease of administration over multiple sites and a relatively short time frame in which it can be administered.

Serum NfL Chain

Serum NfL (sNfL) will be assessed using the Quanterix Simoa platform. This platform has a specialized immunoassay (NF-light) that allows for the detection of neurological biomarkers at very low levels (pg/mL) with excellent consistency and reproducibility. Given the low levels of sNfL, this was the only assay that could be used for this study at the time of study design.

Lymphocyte Subsets

Overview

Lymphocyte subset analysis is a composite outcome that combines the results from 2 separate subset panels. Owing to the real-world nature of this study, the surface marker selection was based on the markers available at the local pathology services. The results are shown in Table 1.

Table 1. Minimum data set from all sites.

Surface marker	Absolute numbers (IU[a])	Proportional values	How proportional data is derived
TBNK[b] panel			
CD45	✓[c]	✓	As per the FBE[d]
CD3	✓	✓	CD45+CD3+ (T cells as a percentage of total lymphocytes)
CD4	✓	✓	CD45+CD3+CD4+ (CD4+ [T helper class] as a percentage of T cells)
CD8	✓	✓	CD45+CD3+CD8+ (CD8+ [cytotoxic T cells] as a percentage of T cells)
CD19	✓	✓	CD45+CD3−CD19+ (B cells as a percentage of total lymphocytes)
CD56/16	✓	✓	CD45+CD56+CD16+CD3− (natural killer cells as a percentage of total lymphocytes)
B memory panel			
CD45	✓	✓	As per the FBE
CD19	✓	✓	CD45+CD19+ (B cells as a percentage of total lymphocytes)
CD27		✓	CD45+CD19+CD27+ (memory B cells as a percentage of total B cells)
Immunoglobulin D		✓	CD45+CD19+CD27+IgD±(class switched or unswitched as a percentage of memory B cells)
CD38		✓	CD45+CD19+CD27+CD38+ (proportion of plasmablasts as a percentage of memory B cells)

[a]IU: International Units.

[b]TBNK: T cells, B cells, and natural killer cells.

[c]Tick marks indicate where the subset will be presented as absolute numbers (column 2) or as proportional values (column 3).

[d]FBE: full blood examination.

T Cells, B Cells, and Natural Killer Cells Panel

T cells, B cells, and natural killer cells (TBNK) panel will be evaluated at each site using the standardized TBNK cocktail from Becton Dickinson. All sites will use the same antibody cocktail for this panel. All results are presented as absolute numbers and percentages of total lymphocytes. Raw flow cytometry data will be obtained from all sites, and concordance measures will be performed to ensure that the reporting of total cells and subsets of cells is consistent between the sites.

B Memory Panel

The second panel will evaluate the B memory cell compartment using antibodies raised against CD45, CD19, CD27, immunoglobulin D, immunoglobulin M, CD21, CD24, and CD38 surface antigens. The minimum panel is gated on the lymphocyte population and assesses CD19, CD27, immunoglobulin D, and CD38. Table 1 lists the minimal data set for each site.

DNA Methylation

Epigenome-wide DNA methylation will be evaluated using DNA extracted from frozen whole blood samples. Genomic DNA will be bisulfite converted and hybridized to Illumina Infinium MethylationEPIC BeadChip arrays at the lead site. Changes in DNA methylation (differentially methylated positions) will be expressed as population medians. Medians will be used to identify changes between responders and nonresponders that meet both the significance cutoff of $P<.05$, and a threshold of >10% change.

RNA or Gene Expression Analysis

RNA will be collected in PaxGene tubes and stored for future analysis, as per funding.

End Points and Outcomes

Participants will attend visits or receive phone calls for assessments at baseline (before 1st dose) and months 1 (before 2nd dose), 3, 7, 12 (before 3rd dose), 13 (before 4th dose), 18, 24, 30, 36, 42, 48, 54, 60, 66, and 72 months, and a variable time point (Tv; at exacerbation of disease and/or before change in treatment or redosing). The schedule of the assessments is shown in Multimedia Appendix 1. BICAMS will be performed annually. MRI will be performed yearly, plus one additional scan 6 months after the first treatment course. Lymphocyte subsets (TBNK and B memory panels) will be performed at screening and at 3, 7, 12, 18, 24, 36, 48, 60, 72, and Tv. Serum NfL will be assessed at screening and at 3, 7, 12, 18, 24, 36, 72, and Tv. DNA methylation and RNA collection occur at screening and at 7, 24, 72, and Tv.

End Points

The primary end point for all outcome measures is the proportion of patients with MS achieving NEDA status (responders) at 6-years relative to screening. However,

preliminary end points will also be considered at each of the major biomarker collection points (months 7, 24, 48, and Tv).

The key outcome measures will be NEDA 3 or 4 responders after 6-years. Additional outcome measures will change over time from baseline in MRI parameters (brain volume loss, lesion load, and lesion volume), cognition, lymphocyte subsets, sNfL, and global DNA methylation profiles. In addition, the Tv time point will be used to determine if there are any changes in biomarker status that may predict disease activity. This will be compared with the time point at which the patient is deemed to have stable disease.

Statistical Methods

Sample Size Calculation

This is a longitudinal study of 150 patients with MS entering the study and predicted to have no more than 20% dropout. Over the study period, we expected 120 patients with MS with longitudinal data for all measured factors: clinical, cellular, and omics. On the basis of CLARITY and CLARITY extension study data, we expect approximately 50% of patients with MS (n=60) to exhibit disease activity according to NEDA 3 (ie, nonresponders) [7-10].

We performed a detailed simulation analysis to assess the power of our sample sizes to detect significant associations at a range of effect sizes and for a range of significance thresholds as per the recommendations of Tsai and Bell [45]. With 120 cases (60 responders vs 60 nonresponders), this study will have 80% power to detect a minimum mean biomarker difference of 10% at a Benjamini-Hochberg false discovery rate of 0.05, which will reasonably balance type I and type II errors. To detect more minor differences, we will use a penalized regression analysis within a machine learning framework using the GLMNet tool [46]. This method is designed for studies with large numbers of predictors and will further enhance the power to identify multi-marker signatures that are predictive of patient response (see details below in the *Association Modeling* section).

Missing Data

The trial data set comprises multiple outcome assessments made for each subject over a 72-month period. Therefore, because of the longitudinal nature of the data and the lengthy follow-up period, it is likely that missing outcome data will be present because of loss to follow-up. Patterns and degrees of missingness will be summarized and will inform the approach taken to deal with missing data (eg, missing at random analysis).

Association Modeling

Our primary outcome is treatment response status according to NEDA 3. We will perform parametric statistical analysis to determine whether any clinical parameters are associated with outcome—the dependent variable. Multiple repeated measurements of the same individual will be obtained. Therefore, we will apply generalized linear mixed models for binary outcomes, with random effects for time points to account for within-subject correlations and clustering. Clinical factors included in the primary analysis will be EDSS, MRI, and relapse rate measures regressed at baseline. Confounding factors (age, sex, disease duration, etc) will be included as required. By carefully defining covariate values in terms of lagged or leading indicators of study factors, longitudinal data will help us to establish the direction of causation and any lags involved. We will also use Mendelian randomization techniques to help dissect causation from the correlation of evidence for causality. In this analysis, all predictor biomarker variables will be modeled individually and yield a test-specific (unadjusted) *P* value. However, we will apply a Benjamini-Hochberg false discovery rate to adjust the raw *P* value for multiple testing while maintaining power. The secondary outcome variables will be modeled similarly using mixed models with specific parameters dependent on the type of data.

To identify multi-biomarker signatures that predict response in this patient cohort, we will also use machine learning algorithms on the patient cohort data set. Specifically, elastic-net regularized generalized linear model analyses using logistic, linear, or multinomial or Poisson models (depending on the outcome variable) will be conducted within a cross-validation routine to avoid overfitting. This will be performed on the entire factor set using the GLMNet package in the R program [46]. Briefly, GLMNet fits a generalized linear model via penalized maximum likelihood and is akin to a stepwise forward regression with the added feature of being able to perform internal cross-validation. GLMNet allows for both binary and multinomial outcomes. GLMNet allows for the rapid discovery of reduced factor panels that are likely to be associated with outcomes. This complementary approach is not susceptible to multiple testing burdens and will facilitate the identification of the best fitting multifactor signature that is predictive of treatment response [46].

The first analysis time point will be the 6-month assessment, which will be analyzed at this stage. The full data set up to and including the 6-month assessment will be subject to appropriate data cleaning for all variables involved in the primary analysis, consisting of postentry validation checks, and assessing the data for outliers.

Additional interim analysis will be completed at 24 months, 48 months, and again at study termination when all data have been collected.

Results

Funding

This study was funded in October 2018 as an investigator-initiated trial by Merck Healthcare Pty Ltd, KGgA, Darmstadt, Germany, to the lead site (John Hunter Hospital).

Ethics Statement

This study is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000257167) with Universal Trial Number (U1111-1228-2165). Ethical approval for conducting this study was granted on November 8, 2018, by the Hunter New England Local Health District Human Research Ethics Committee (protocol 2019/ETH08849). The study will be conducted in accordance with the revised Declaration of Helsinki, and all participants will provide written informed consent to participate in this study.

Enrollment

As of May 2021, 145 participants have been enrolled in the study. Recruitment was completed by June 2021, and the study is expected to conclude in 2027.

Discussion

Principal Findings

Our study is designed to collect real-world outcomes, while filling the gaps of the previous randomized controlled trials (RCTs) of cladribine tablets for the treatment of MS. This study also offers the opportunity to assess the long-term use of cladribine tablets in a clinical setting and the effectiveness of additional courses of cladribine tablets based on disease activity, in ongoing treatment of MS.

RCTs are the *gold standard* for evaluating treatment outcomes and providing efficacy data for new treatments. However, the strict inclusion criteria and protocol-driven approach may lead to low generalizability because these trials are not always reflective of real-life care [47,48]. In addition, the frequency of MRI in MS RCTs is often higher than that in routine clinical practice [47,48]. Real-world studies can complement data from RCTs by investigating patients who are receiving treatment and being monitored according to routine clinical practice [47,48], and the importance of real-world clinical data is becoming increasingly recognized. For example, MSBase, which is now following over 70,000 patients with MS worldwide with regular assessments, has shaped clinical decision-making in the MS field over the past 5 years using real-world data [49].

The exclusion criteria for this study are deliberately minimal, so that most patients with MS who are planning to commence or choose to take cladribine tablets as part of their routine MS clinical care, are eligible to participate. This study imposes no limits on prior DMT exposure or immunosuppression, no upper limit on EDSS, and an upper age limit of 70. These relaxed inclusion criteria will allow us to capture the broadest range of patients with MS possible, and with the generation of data sets that are reflective of *real-world* MS demographics.

In the CLARITY study, 75% of the participants were treatment-naïve before entering [7]. As with all pharmaceutical trials, there were restrictions on prior DMT use (no more than two failed DMTs were allowed before study entry, and anyone who had used prior immunosuppression was excluded) [7]. This leaves a scarcity of data relating to how patients with MS who have been on prior DMTs, particularly immune suppressants with long-term effects such as alemtuzumab or even dimethyl fumarate, will respond to cladribine tablets. In addition, this does not reflect clinical reality, where many patients with MS have trialled several treatments and often failed several other DMTs before starting cladribine tablets. Data on the safety and effectiveness of cladribine after other DMTs are needed for clinicians and patients with MS to be able to make appropriate decisions about therapy, particularly if they are switching from a prior immunosuppressant. Our study is well-positioned to provide such data.

This trial will also investigate the effectiveness of additional courses of cladribine tablets based on disease activity. Alemtuzumab, another immunomodulatory therapy, is administered in a similar dosing scheme to cladribine tablets [12]. In the CARE-MS II trial, up to four additional courses of alemtuzumab were given to patients with MS as required, with success [5]. Starting in year 3, if patients with MS in this trial have a clinical or radiological relapse, they will be offered an additional course of cladribine. Although the CLARITY extension trial found that additional courses provided no additional benefit, these courses were not offered based on disease activity [9]. This will be the first investigation into an additional cladribine dose based on disease activity.

There is evidence that clinicians are shifting their treatment goals away from relapse free to achieving NEDA status. For example, a recent study using MSBase data demonstrated that just one new subclinical T2 lesion was associated with 1.62 times odds of changing treatment compared with no new lesions [50]. Patients with MS taking cladribine tablets achieved 47% NEDA 3 rates in CLARITY after 2 years [7]; however, rates of NEDA 4 and data beyond 2 years have not been reported. The addition of accelerated brain volume loss to the NEDA criteria (NEDA 4) is an important parameter as it has been shown to be predictive of long-term disability progression and cognitive decline [26,51]. This is highlighted in the FREEDOM trials, where 31% of patients with MS on fingolimod sustained NEDA 3 status, but only 19.7% achieved NEDA 4 after 2 years [16].

Achieving NEDA status may also differ outside the bounds of RCTs. A real-world study conducted in the USA (MS-MRIUS) evaluated nearly 600 patients with MS on fingolimod and found that NEDA 3 was achieved in approximately 58.7% of patients with MS, and 37.2% had achieved NEDA 4 [52]. The differences may be because of the shorter follow-up time (16 months vs 24 months), different patient populations (less severe disease course), or may be reflective of the real-world nature of the data collection versus an RCT [52]. Another real-world study also reported slightly higher levels of NEDA 3 (44%) after 2 years, but did not evaluate NEDA 4 [53]. There has been one small study of cladribine tablets from MSBase data, which compared outcomes over 1 year [54]. Although this study was shorter than CLARITY, the data were similar, with effects lasting at least 4 years [54] despite the majority of patients with MS receiving only one course of treatment. The MSBase study did not specifically report on NEDA 3 outcomes; therefore, it will be interesting to see if NEDA rates remain the same for cladribine use in the clinical setting.

There have been recent criticisms of the current NEDA criteria [55-57]. Stangel et al [57] suggested an algorithm that incorporates cognitive (SDMT), patient-reported outcomes, depression and anxiety ratings, and other parameters. Other criticisms suggest that biomarkers of inflammation and neurodegeneration in body fluids need to be added for a true reflection of disease activity (NEDA-5 or minimal evidence of disease activity) [56]. The inclusion of blood-based biomarkers in this study, including sNfL, as well as cognitive assessments (the BICAMS includes the SDMT) will ensure that we are also able to assess disease activity based on these parameters and assess NEDA5 or minimal evidence of disease activity when a consensus is reached. Furthermore, the discovery of biomarkers that may indicate a response to treatment may allow us to

prevent patients with MS from undergoing life-long immune suppression if not required. This could be translated to other MS therapies.

There are minimal real-world data on the effectiveness of cladribine tablets for MS. This study will not only fill this knowledge gap, but also evaluate the efficacy of a clinically indicated additional course beyond the year 2 course. The regular collection of biospecimens for biomarker assessment will help identify biomarkers that may be indicators of treatment response and the need for additional dosing. This may help move clinical practices toward individualized dosing schedules.

Data Sharing Statement

Deidentified individual data sets will be available upon request to the authors following the publication of the results of the study.

Conflicts of Interest

VEM has received honoraria for presentations from Biogen and Merck Healthcare Pty Ltd. She received research funding from Merck KGgA and Biogen. RAL has no conflicts of interest. For author MM, her institute and health service receives funding from Merck KGaA. MFP has received travel sponsorship from Merck KGaA. KB has received honoraria for presentations and/or educational support from Roche, Biogen, Sanofi Genzyme, Teva, Novartis, and Merck KGaA and has served on advisory boards for Merck and received research funding from BioCSL. TK served on scientific advisory boards for Roche, Sanofi Genzyme, Novartis, Merck KGaA, and Biogen; steering committee for Brain Atrophy Initiative by Sanofi Genzyme; and received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi Genzyme, Teva, BioCSL, and Merck KGaA and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene, and Merck KGaA. AGK has recently received speaker honoraria and scientific advisory board fees from Bayer, BioCSL, Biogen-Idec, Lgpharma, Merck KGaA, Novartis, Roche, Sanofi-Aventis, Sanofi Genzyme, Teva, NeuroScientific Biopharmaceuticals, Innate Immunotherapeutics, and Mitsubishi Tanabe Pharma. BT has received travel assistance from Merck KGaA, Novartis, and Biogen-Idec and served on Ad Boards for Merck, Sanofi, Novartis, and Biogen. SH has received honoraria for consultancy, travel, and speaking fees from Emmanuel Merck, Darmstadt, Serono, Bayer, Biogen, Sanofi, Atara, and Novartis. PM received honoraria and travel grants from Biogen, Sanofi Genzyme, Novartis, and Merck KGaA. HB serves on steering committees and scientific advisory boards for Merck KGaA, Biogen, Novartis, and Roche. He received conference travel support from Merck KGaA. The institution has received honoraria for speaker engagements for Merck KGaA, Biogen, Roche, and Novartis. The institution has received research support from Biogen, Roche, Merck KGaA, Novartis, National Health and Medical Research Council, Medical Research Future Fund, Trish Foundation, and Multiple Sclerosis Research Australia. HB also receives personal compensation for serving the Brain Health Initiative Steering Committee. MB has received institutional support for research, speaking, and/or participation in advisory boards for Biogen, Merck KGaA, Novartis, Roche, Sanofi Genzyme, and Bristol Myers Squibb. He is a co-founder of RxMx and Research Director for the Sydney Neuroimaging Analysis Centre. For author JLS, the institution receives nondirected funding as well as honoraria for presentations and membership on advisory boards from Sanofi Genzyme, Biogen, Merck KGaA, Teva, Roche, and Novartis Australia.

Multimedia Appendix 1

Study overview. Schedule of visits for study duration. The shaded area indicates when each study assessment was performed. Tv=clinical deterioration, Tv+=one month post redose (if applicable), Time point T15* month number is dependent on the year 2 dose (3 months post year 2 week 1). The Brief Cognitive Assessment for Multiple Sclerosis assessment will alternate between the standard and alternate versions. **Indicates magnetic resonance imaging scans to be used only if clinically applicable. X denotes the major analysis time point.

[PNG File , 46 KB - resprot_v10i10e24969_app1.png]

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Abbreviations

BICAMS: Brief Cognitive Assessment for Multiple Sclerosis
CARE-MS Study: Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis Study
DMT: disease-modifying therapy
EDSS: expanded disability status scale
MRI: magnetic resonance imaging
MS: multiple sclerosis
NEDA: no evidence of disease activity
NfL: neurofilament
RCT: randomized controlled trial
SDMT: Symbol Digit Modalities Test
TBNK: T cells, B cells, and natural killer cells
Tv: variable time point

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Protocol

The Chicago Health and Life Experiences of Women Couples Study: Protocol for a Study of Stress, Hazardous Drinking, and Intimate Partner Aggression Among Sexual Minority Women and Their Partners

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Abstract

Background: Large gaps exist in research on alcohol use and intimate partner aggression (IPA) among sexual minority women (SMW; eg, lesbian, bisexual). Dyadic research with SMW and their partners can illuminate how couple-level factors operate in conjunction with individual-level factors to shape well-being in this understudied and vulnerable population. Given the traditionally gendered lens with which women are primarily viewed as victims and men as perpetrators, understanding the dynamics of IPA in same-sex female couples can also advance research and practice related to IPA more generally.

Objective: Guided by a recent extension of the minority stress model that includes relational (couple-level) sexual minority stress and the I-cubed theoretical perspective on IPA, we will collect individual and dyadic data to better characterize the links between hazardous drinking and IPA among SMW and their partners. First, this study aims to examine the associations among minority stress, hazardous drinking, and IPA in SMW and their partners. Minority stressors will be assessed as both individual and couple-level constructs, thus further extending the minority stress model. Second, we aim to examine potential mediators and moderators of the associations among minority stress, hazardous drinking, and IPA. Finally, we aim to test models guided by the I-cubed theoretical perspective that includes instigating (eg, relationship conflict), impelling (eg, negative affect and trait anger), and inhibiting (eg, relationship commitment and emotion regulation) or disinhibiting (eg, hazardous drinking) influences on IPA perpetration.

Methods: This United States National Institutes of Health–funded project will draw from a large and diverse cohort of SMW currently enrolled in the Chicago Health and Life Experiences of Women (CHLEW) study—a 21-year longitudinal study of risk factors and consequences associated with SMW hazardous drinking. SMW currently enrolled in the CHLEW and their partners will be invited to participate in the CHLEW Couples Study. By analyzing dyadic data using actor-partner interdependence models, we will examine how each partner's minority stress, hazardous drinking, and IPA experiences are associated with both her own and her partner's minority stress, hazardous drinking, and IPA perpetration.

Results: Data collection began in February 2021 and will likely continue through 2023. Initial results should be available by mid-2024.

Conclusions: The CHLEW Couples Study will fill important gaps in knowledge and provide the basis for future research aimed at clarifying the causal pathways linking hazardous drinking and IPA among SMW. This will support the development of culturally appropriate targeted individual and dyadic prevention and intervention strategies.

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KEYWORDS

lesbian; bisexual women; intimate partner aggression; partner violence; same-sex couples

Introduction

Background

Intimate partner aggression (IPA) is a serious public health problem that affects more than 1 in 3 women in the United States [1]. Although the definition of IPA continues to be debated [2], we consider IPA to include psychologically, physically, or sexually aggressive or coercive behaviors by a romantic or sexual partner [3]. Research on IPA among sexual minority women (SMW; eg, lesbian, bisexual) is relatively new; this research has primarily focused on heterosexual couples and largely, although not exclusively, on male-to-female aggression [4-6]. However, a growing body of literature suggests that SMW may be at an even greater risk of experiencing IPA than heterosexual women [7-12]. Among women surveyed in the Centers for Disease Control and Prevention's 2010 National Intimate Partner and Sexual Violence Survey, 32% of heterosexual women, 42% of lesbian women, and 57% of bisexual women reported lifetime physical violence by an intimate partner [8]. Rates of psychological violence or aggression were also higher among lesbian (67%) and bisexual (73%) women than among heterosexual women (47%).

Ample research demonstrates strong linkages between hazardous drinking and IPA among heterosexual couples [5,6]. Hazardous drinking, defined by the World Health Organization as a pattern of alcohol use that increases the risk of harmful consequences (operationalized in this protocol using several indicators such as heavy drinking, heavy episodic drinking, and intoxication), is among the most prominent health-related disparities in comparisons of heterosexual women and SMW. Research examining the associations between IPA and hazardous drinking in SMW's intimate relationships is limited [13]. Yet, in our research [14], and others' [15-17], SMW report substantially higher rates of drinking alcohol, heavy drinking, and drinking-related problems than heterosexual women, which may increase the risk of IPA.

Drawing on the sample of SMW enrolled in the 21-year longitudinal Chicago Health and Life Experiences of Women (CHLEW) study, we will recruit the partners of our current participants to examine factors associated with hazardous drinking and IPA in this population. Specifically, we will take an innovative dyadic approach to test the influences of factors known to be associated with IPA perpetration and victimization among women generally (eg, hazardous drinking, relationship conflict, depression, and childhood abuse), as well as sexual-minority-specific factors (eg, sexual identity concealment and internalized stigma), along with new couple-level minority stress constructs that stem from society's stigmatization of same-sex relationships.

Alcohol Use and IPA Among SMW

Research in the general population has typically found a positive association between an individual's drinking pattern and relationship dissatisfaction or IPA [18,19]. For example, a meta-analysis by Cafferky et al [18] indicated a statistically significant association between alcohol use, particularly problematic use, and both perpetration and victimization, replicating the previous 8 meta-analyses that examined alcohol use and IPA. Moreover, because of the expanded number of studies, this meta-analysis demonstrated that the association between alcohol use and perpetration was stronger for men than women, a finding that is consistent with earlier substantive reviews [19]. Although too few to permit meta-analysis, studies of couples' drinking patterns from a dyadic framework have also demonstrated a relationship between alcohol use and relationship satisfaction or intimate partner violence. A number of large-sample longitudinal studies have demonstrated that the lowest satisfaction and the highest risk for divorce are found in couples in which one member is a heavy drinker, and the other is not [20,21]. The association between more nuanced measures of couples' drinking patterns and intimate partner violence is somewhat more complicated, although it appears that heavy drinking by either member of the couple or by both is associated with an increased risk of IPA [22-24].

In contrast to studies among heterosexual couples, the few studies on alcohol use and IPA among SMW have largely been descriptive and have had multiple methodological limitations (eg, samples that overrepresent younger White participants or are too small or homogenous for subgroup analyses, lack of guiding theoretical frameworks or perspectives, and lack of dyadic research) [20,23,24]. Thus, the links between SMW's drinking and IPA are poorly understood. We know that hazardous drinking may contribute to or be an indicator of relationship stress and conflict in SMW's relationships similar to heterosexual relationships. For example, Kurdek [25] asked same-sex couples to rate the issues about which they fought the most, such as finances, sex, and household tasks. Among same-sex female couples, the most frequent disagreements were about drinking or smoking [25]. Drabble and Trocki [15] found that SMW were almost 11 times as likely as heterosexual women to report relationship or social problems (eg, fighting and partner

being angry) related to their drinking. Kelley et al [26] found that, controlling for psychological and physical aggression, lesbian women who reported discrepant alcohol use between themselves and their partners also reported poorer relationship quality.

A further limitation of research on the links between alcohol use and IPA among SMW is that it has typically focused on experiencing but not perpetrating IPA. For example, using data from the California Health Interview Survey, Goldberg and Meyer [27] found that both SMW and heterosexual women who binge drank on a daily or weekly basis had significantly higher odds of having experienced IPA. Research on the perpetration of IPA among SMW has tended to focus on discrepancies in drinking between partners as a potential causal factor. For example, in a longitudinal study of lesbian women, discrepant drinking was prospectively associated with being psychologically but not physically aggressive at 6- and 12-month follow-ups [28]. Being physically or psychologically aggressive at baseline was additionally associated with discrepant drinking. Thus, theoretically grounded research that includes both general and sexual minority–specific risk factors and that examines both IPA perpetration and victimization from the perspective of each partner is needed.

Guiding Theoretical Perspectives

Minority Stress Theory

The predominant explanatory theory for health disparities among SMW is minority stress, which derives from the broader conceptualization of social stress as potentially harmful to health [29-31]. Sexual minority individuals are exposed to unique stressors on a continuum of proximity to the self. Most distal are objective stressors based primarily on the environment, such as discrimination and prejudice. These lead to more proximal appraisals of the environment as threatening, resulting in expectations of rejection or stigma. Most proximal are internalizations of negative social attitudes toward sexual minorities (internalized stigma) and the concealment of a sexual minority identity. As these stressors tax the ability to function on a day-to-day basis, they are associated with poorer psychological well-being and unhealthy coping behaviors [29,32-34], such as hazardous drinking [35] and possibly IPA [13,36].

In a systematic review of IPA and sexual minority–specific stressors, Longobardi and Badenes-Ribera [11] identified 10 studies of minority stress and same-sex IPA perpetration and victimization published between 2005 and 2015. The results indicated that internalized stigma, stigma consciousness, sexual identity concealment, and experiences of discrimination were each associated with both victimization and perpetration of IPA. However, the effect sizes for these associations were small to medium [37]. In a meta-analysis of risk factors for IPA perpetration and victimization, Kimmes et al [10] found internalized homophobia to be one of the strongest risk factors for IPA perpetration but not victimization among same-sex couples. Similar to research on other risk factors for same-sex IPA, nearly all studies of minority stress and IPA have focused on individual-level experiences. People in same-sex relationships, as well as those in other stigmatized relationship forms (eg, interracial or interethnic or intercultural couples), are exposed to both individual-level and couple-level minority stressors. For example, an SMW may hide her lesbian or bisexual identity from family members or friends who are perceived to be homophobic (individual-level minority stressor). However, when she is in a relationship with another woman, her status as a member of a sexual minority couple will result in exposure to additional stressors beyond those experienced at the individual level. For instance, she and her partner must jointly manage the visibility of their relationship and the possibility of rejection of them as a couple by families, religious communities, neighbors, and friends (couple-level minority stressor). This extension of the minority stress model to include couple-level stressors supports a more comprehensive examination of minority stress than its original conceptualization. A greater understanding of couple-level minority stress and its impact on hazardous drinking and IPA will provide important information that can inform couple-level interventions.

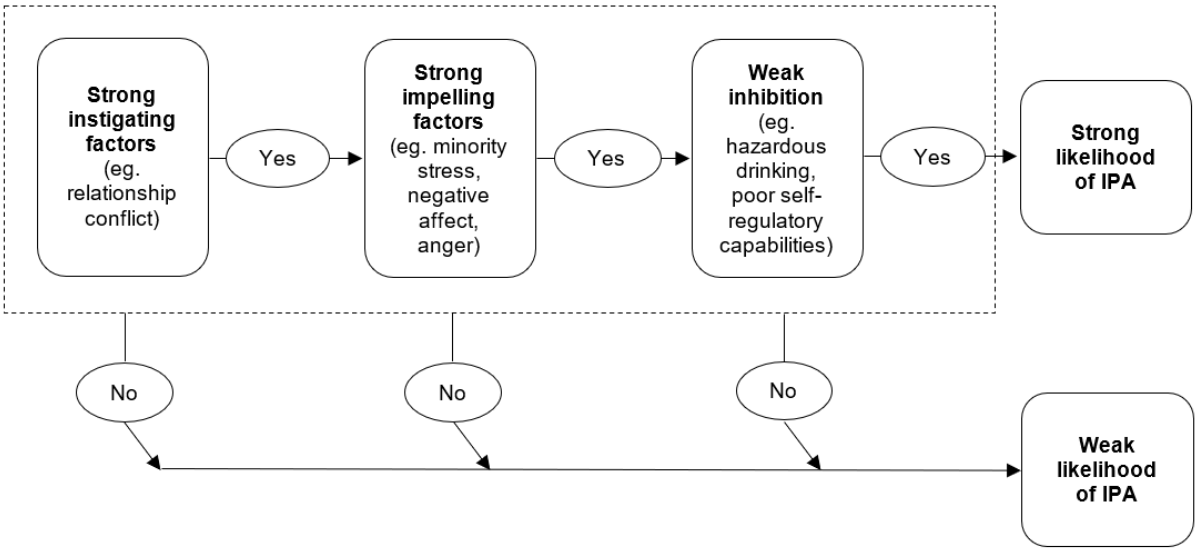
I-Cubed Model of IPA Perpetration

Decades of research has documented the impact of alcohol use on aggressive behavior. Generally focused on laboratory experiments of aggression between males, this literature has demonstrated that administering alcohol resulted in higher levels of aggression than administering no alcohol or a placebo [38] and that greater consumption of alcohol led to higher levels of aggression [39]. Explanations of alcohol's effect on aggression centered on the cognitive disruption caused by intoxication; theorists argued that alcohol intoxication impairs an individual's ability to attend to and process cues in a situation, resulting in *alcohol myopia*, in which behavior is more strongly affected by the dominant cues in the situation [40,41]. When cues are facilitative of aggression, alcohol consumption increases the likelihood of aggression; however, when cues are neutral or inhibitory, alcohol may, in fact, decrease the likelihood of aggression. In the context of aggressive cues, alcohol impairs cognitive functioning and reduces a person's ability to self-regulate emotions and behavior. This, in turn, may impair the ability to restrain aggressive impulses. There is substantial support for this model of alcohol-related aggression [42].

To evaluate potential inhibitors or disinhibitors in the associations between hazardous drinking and IPA, we draw on the I-cubed (I^3) model of IPA perpetration. This model incorporates the alcohol myopia theory into a larger framework for understanding the process by which a given factor promotes or mitigates aggression as well as how multiple factors interact to increase or decrease the aggression-promoting tendencies of the factor [43-45]. Results from experimental and longitudinal studies provide strong support for the I^3 perspective and underscore the importance of self-regulatory processes in helping to reduce the risk of IPA. As illustrated in Figure 1, instigating triggers, such as relationship conflict, can set the stage for aggressive behaviors in a couple. For example, if the partner who experienced the instigating trigger also experiences high levels of minority stress or has a tendency to become angry easily (impelling factor), they will be more likely to respond aggressively. However, there are other factors that can act to

inhibit aggression (eg, relationship commitment and emotion regulation) or act as disinhibitors (eg, alcohol consumption). We will test models that include both general factors stemming from the I^3 framework and sexual minority–specific stressors (both individual and couple level) within a dyadic framework to understand how a diverse array of variables influence hazardous drinking and its association with IPA among SMW and their partners.

Figure 1. I-cubed theoretical perspective on intimate partner aggression perpetration among sexual minority women. IPA: intimate partner aggression.



Testing Dyadic Models Derived From Minority Stress and I3 Models

Research on IPA has historically taken a gendered perspective (women as victims or men as perpetrators), and for the most part this research has concentrated on either victims or perpetrators, not both simultaneously. Moreover, research on the links between hazardous drinking and IPA has rarely focused on the effects of both partners' alcohol use. However, findings from existing studies (all with heterosexual couples) suggest that each partner's alcohol use can independently predict both partners' physical IPA perpetration. For example, Cunradi et al [46] found that among White and Black couples in which the female partner had alcohol-related problems, rates of female-to-male IPA were five to six times higher than in couples in which the female partner did not have alcohol problems. Among couples in which the male partner had alcohol problems, the risk of female-to-male IPA was 3 to 4 times higher than among couples in in which the male partner had no alcohol problems. These researchers found that among Hispanic couples, women's alcohol problems were not associated with IPA perpetration. However, among Hispanic couples in whom the male partners had alcohol problems, the odds of IPA perpetration were more than 2 times higher than in couples in whom the male partner had no alcohol problems. Other research among heterosexual couples suggests that one partner's heavy episodic drinking predicts the other partner's anger (partner effects), and both actor and partner alcohol use predict physical and psychological IPA [47-49].

There is almost no dyadic research on hazardous drinking among sexual minority couples. In the only published study of which we are aware, LeBlanc et al [50] reported that in a sample of same-sex male and female couples, participants who felt that their relationships were not recognized to the same extent as the relationships of heterosexual couples (a couple-level minority stressor) had higher rates of problematic drinking. Moreover, results showed both actor and partner effects: one partner's perceived unequal recognition was positively associated with the other's problematic drinking [44].

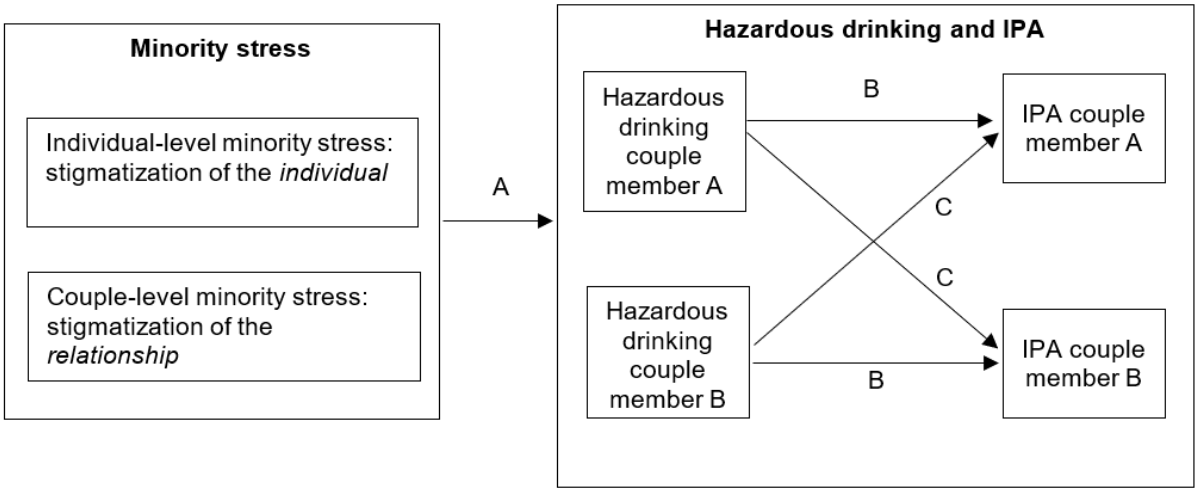
Less well-understood are mediators and moderators of the hazardous drinking–IPA link, which is important for identifying modifiable mechanisms that may be used in prevention and intervention efforts. Although there has been research on mediators or moderators of the associations between alcohol use and violence, as noted above, much of it has focused on violence between men. Far less research is focused on couples. Research in this area tends to focus almost exclusively on factors that influence alcohol use and IPA in heterosexual couples [51]. For example, relationship dissatisfaction seems to play a mediating role in this link among heterosexual couples [51,52]. Among women in heterosexual couples reporting bidirectional violence, wanting to appear tough or wanting to intimidate one's partner mediated the link between alcohol misuse and IPA. However, self-defense and the need to express negative emotions did not [53]. Whether the mediators and moderators of the associations between hazardous drinking and IPA are similar in SMW relationships is not yet known.

Although all SMW are exposed to minority stress, most do not perpetrate or experience IPA—even in the context of hazardous drinking—so there are clearly other factors that influence the risk of IPA in this population. Some evidence suggests that among women aggressors in heterosexual relationships, stress interacts with coping styles to increase aggressive behavior, and stress and coping may moderate the association between

alcohol use and IPA [54]. Among lesbian women, general stressors have been found to be positively associated with hazardous drinking, and hazardous drinking is associated with IPA. Those who reported higher levels of emotional distress were more likely to drink to cope, consume more alcohol, and experience more drinking-related problems [55]. In a sample of lesbian women, Mason et al [56] found links between minority stress and physical IPA perpetration and that negative affect and interpersonal intrusiveness (eg, possessiveness) mediated this association.

Together, these findings suggest that hazardous drinking may be an important contributor to IPA perpetration in SMW's relationships, particularly among couples who experience high levels of minority stress. They also highlight the importance of examining alcohol-related IPA (inclusive of both partners' reporting of perpetration and victimization) within a dyadic framework and potential mediators and moderators of these associations. For example, as illustrated in Figure 2, both individual- and couple-level minority stressors may influence the experiences of hazardous drinking and IPA perpetration among SMW and their partners (pathway A). The B pathways illustrate the hypothesized association between hazardous drinking and IPA perpetration for individual couple members (actor effects). The C pathways illustrate partner effects (the effects of each member's hazardous drinking on their partner's IPA perpetration).

Figure 2. Extending the minority stress framework to include couple-level stressors. IPA: intimate partner aggression.



Aims

The specific aims of the study are discussed in the following sections.

Aim 1

Our first aim is to examine cross-sectional associations among minority stress, hazardous drinking, and IPA (perpetration and victimization) in SMW and their partners. We will test bivariate associations between hazardous drinking and IPA, and between individual- and couple-level minority stressors and hazardous drinking (heavy drinking, heavy episodic drinking, intoxication, and symptoms of potential alcohol use disorder) and IPA (physical, emotional or psychological, and sexual).

Aim 2

Our second aim is to examine potential mediators and moderators of the associations between minority stress and hazardous drinking and IPA (perpetration and victimization). Using dyadic actor-partner interdependence models (APIMs) and controlling for key variables, we will test potential mediators (eg, relationship conflict) and moderators (eg, relationship status and coping) of the associations between minority stress and hazardous drinking and IPA among SMW and their partners. We will also investigate whether the associations between hazardous drinking and IPA differ by sexual identity and race or ethnicity, as well as whether key psychosocial resources (eg, social support and positive coping) mediate the associations between minority stress and both hazardous drinking and IPA.

Aim 3

Guided by the I^3 theoretical perspective, we will test models that include instigating factors (eg, relationship conflict), impelling factors (eg, minority stress, negative affect, and trait anger), and inhibiting (eg, relationship commitment and emotion regulation) or disinhibiting (eg, hazardous drinking) factors on IPA perpetration. Using dyadic data, we will examine a highly interactive model in which IPA perpetration is modeled as a function of both actor and partner minority stress, factors such as relationship conflict or commitment and hazardous drinking, and actor-partner interaction effects that take into account important areas of discordance (eg, differences in partners' drinking patterns or experiences of minority stress) [22,57]. The models will control for key sociodemographic (eg, age, sexual identity, race or ethnicity, and length of relationship) variables.

Methods

Overview

In the baseline CHLEW study (wave 1; K01AA00266), we collected comprehensive data from a large and diverse sample

of SMW who resided in the greater metropolitan Chicago (United States) area. This mostly descriptive study replicated and extended the National Study of Health and Life Experiences of Women (R01AA004610, SCW, PI), a 20-year longitudinal study of drinking patterns, problems, risk factors, and consequences among adult women in the general US population. Since wave 1, four follow-up waves of the CHLEW have been funded (R01AA013328-14, TLH, PI). Wave 2 extended the CHLEW to examine changes in alcohol use patterns and risk and protective factors for hazardous drinking, wave 3 examined the impact of accumulated childhood and adult stressors on drinking outcomes among SMW, and waves 4 and 5 (currently underway) focus on the impact of legalization of same-sex marriage in the United States on hazardous drinking and health. The procedures for each wave have been reviewed and approved by the institutional review board of the university where the principal investigator (TLH) held her primary appointment (waves 1-5 by the University of Illinois at Chicago; waves 4 and 5 and this study by Columbia University). Detailed information about the CHLEW study methods can be found elsewhere [58,59].

CHLEW Couples Study Design and Sample

We will draw on the large cohort of SMW currently enrolled in the longitudinal CHLEW study for the recruitment of participants. Approximately half of the CHLEW cohort has been followed since 2000 and a half since 2010. We recruited the wave 1 baseline sample using social network or snowball sampling strategies with additional efforts to maximize sample representativeness. Women were eligible if they were aged ≥18 years, lived in the greater Chicagoland area, and self-identified as lesbian. Unlike most previous studies, participants (N=447) represented a wide age range (18-83 years), and more than half were women of color. In wave 2**,** we successfully located and reinterviewed 86% of the participants. In wave 3**,** we reinterviewed nearly 80% of all original participants (we were able to locate 85% of the women). In wave 3 (2010-2012), we also recruited a supplemental sample (N=373) of younger (aged 18-25 years), Black, Latina, and bisexual women.

As noted above, the sample was quite diverse in terms of race or ethnicity (35.9% Black, 23.1% Latinx, and 37.4% White). We will invite all CHLEW participants who currently have partners to participate in the CHLEW Couples Study. To determine eligibility, each CHLEW participant will be asked if they are dating or in a committed relationship of at least 3 months with an English-speaking partner aged ≥18 years. CHLEW participants will be asked to invite their eligible partners to participate with them in the CHLEW Couples Study. During the course of the CHLEW study, many participants have changed their sexual or gender identity; we will include otherwise eligible participants regardless of sexual or gender identity.

Participant Recruitment and Retention

To aid retention in the longitudinal CHLEW parent study, participants have provided their social security numbers, cell phone numbers, and email addresses and listed the names, addresses, and phone numbers of 4 people who would always know their whereabouts. Letters with return postcards requesting address updates are sent to all participants at 6-month intervals. Other retention strategies included birthday and holiday cards, reminder calls before interview appointments, and graduated monetary incentives—from US $35 in wave 1 to US $80 in this study (US $40 for the telephone interview, US $20 for the web-based self-administered survey, and US $20 if the participant and their partner can be interviewed within 7 days of each other). Of the 820 participants enrolled in CHLEW (as of the writing of the grant application for this study), 49 (6.0%) were deceased, dropped out of the study, or were unable to participate for health reasons, leaving a sample size of 771 (94.0%) [59].

In previous CHLEW surveys, 61%-69% of participants reported that they were in a committed relationship; partial data from wave 4 (underway when the grant application was submitted) indicated that at least an additional 10% were in dating relationships. Although it is possible that the proportion of participants in relationships will be lower in the proposed study, we expect that it will be the same or possibly higher (given marriage equality and improved societal attitudes about sexual minority people and same-sex partnerships). Therefore, we estimate having a recruitment pool of at least 405 (71% of 771) CHLEW participants. In waves 4 and 5 of the longitudinal study, we asked all participants whether their partner (if they had one) was interested in participating in the CHLEW Couples Study. Again, using partially collected data from wave 4, we found that <10% said *no*. On the basis of a conservative estimate of 12% refusals, our sample would be 357 couples. However, CHLEW includes approximately 50 couples (100 women reported that their partner was also in the study), which reduces the estimated sample size to 307 couples. Of these, we expect that a few partners will not meet the eligibility criteria (age ≥18 years and able to speak English). Therefore, we budgeted for a total of 302 couples (604 individual interviews).

Procedures

All SMW enrolled in the CHLEW parent study will receive an invitation from the principal investigator, describing the CHLEW Couples Study. Those in relationships of at least 3 months, whose partner is aged at least 18 years, and who can complete an interview in English will be invited to participate. The invitation letter will include a description of the study procedures, information about incentives (US $60 for each partner, plus an additional US $20 each if the couple agrees to be interviewed in the same week), and will emphasize confidentiality (eg, each member of the couple will have a different interviewer; no information from the interview will be shared with the participant's partner or anyone outside the study team). In the invitation letters, CHLEW participants will be asked to call, text, or send an email message to the research office to indicate their interest. They will also be asked to have their partner contact the research office so that they can be screened and enrolled if eligible. If a partner does not contact the research office within 1 week, a member of the research staff will contact the index CHLEW participant to reassess the couple's interest in participation. Participation will include a one-time, 60- to 90-minute telephone or videoconference interview conducted by a trained interviewer and a 25-minute web-based survey to be completed within 1 week of the

telephone interview. We will ask each member of the couple to refrain from sharing information about the interview or survey until both partners complete the study.

We have collected data using interviews (face-to-face in waves 1 and 2 and telephone or Zoom in waves 3-5; we also completed approximately 100 wave 3 interviews by phone because many study participants had moved outside the Chicago Metropolitan area) as the primary mode of data collection. We feel that these interactions are key to our ability to retain such a high number of participants for 21 years. To assess potential mode effects in wave 3, we compared self-reports of alcohol and drug use among participants interviewed in person with those interviewed by telephone. Although women interviewed by telephone were less likely to report the use of cocaine, we found no differences in any of the hazardous drinking measures. These findings were consistent with the assessments of the 1990 and 2000 National Alcohol Surveys [60,61]. Our finding of limited mode effects in wave 3 provided confidence that this would not significantly influence the self-reports of key variables. Further, in wave 4, we asked participants how they preferred to be surveyed in the future (ie, phone, video, or on the web), and most people had no preference. We moved scales that are of interest but not central to the study's aims to a web-based module to reduce possible participant fatigue associated with a long telephone or Zoom interview (Tables 1 and 2).

Table 1. Demographic questions.

Demographic	Number of items	Description of measure and method of administration	Role in study	Development and modifications
Sexual identity	1	Response options include only lesbian, mostly lesbian, bisexual, mostly heterosexual, only heterosexual, pansexual, queer, asexual, or none of the above. Participants are asked to specify a different term if "none of the above" is chosen. [Interview]	• IV[a] • Covariate	Adapted from Skrocki [62]—revised to be inclusive of additional identities (eg, pansexual and asexual)
Sexual attraction	1	Response options include attracted to women, attracted to men, attracted to people with nonbinary identities, attracted to people of other genders, my attraction to people is not based on gender, not attracted to people of any gender, and not sure. Participants are asked to check all that apply and specify another term if "attracted to people with other genders" was selected. [Interview]	• IV • Covariate	Adapted from Skrocki [62]—revised to be inclusive of attractions other than to women or men
Sexual behavior	2	Past year sexual relationships with people other than the current partner (the partner who is also participating in the study). Response options include relationships with a woman or women, man or men, or nonbinary persons. [Interview]	• IV • Covariate	Adapted from Skrocki [62]—revised to be inclusive of relationships with nonbinary individuals
Sex or gender	1	We first ask about sex assigned at birth, then about current gender. Response options include female, male, transgender man or FTM[b] transgender, nonbinary or genderqueer, and another gender identity. Participants are asked to specify a term if another gender identity is chosen. [Interview]	• IV • Covariate	Follows recommendations presented by Suen et al [63]
Race or ethnicity	2	We first ask about ethnicity (ie, Hispanic, Latina, Latinx, and Latino) and the second about race (response options include African American or Black, Asian or Pacific Islander, American Indian or Alaska Native, White, biracial or multiracial, and another race or ethnicity). If none of these apply, participants are asked to specify their racial or ethnic identities. [Interview]	• IV • Covariate	On the basis of questions asked in the 2010 census
Relationship status	1	In a committed relationship not living together, committed relationship living together, not in a committed relationship, or other; participants are asked to specify if "other" is chosen. [Interview]	• Covariate	Adapted from Hughes et al [64]
Marital status	1	For participants in a committed relationship, response options include legally married, in a domestic partnership or civil union, or not married or in a domestic partnership or civil union. [Interview]	• Covariate	From previous CHLEW[c] waves
Education level	1	No formal schooling, eighth grade or less, some high school, high school diploma or GED[d], some college or 2-year degree, bachelor's degree, graduate or professional school [Interview]	• Covariate	Adapted from Hughes et al [64]
Annual household income	1	"Looking at hand card #18, which of these groups represents your total annual household income from all sources? Household means everyone living in your house that you consider part of your family. Don't include a roommate or housemate." Response options include under US $1000 to US $9999 to >US $200,000 [Interview]	• Covariate	From previous CHLEW waves
Managing finances as a couple	2	Two questions about how finances are managed as a couple; the first asks about each partners' contribution to the total household income, and the second asks who decides how household income is used [Interview]	• Covariate • Moderator	Developed for the CHLEW Couples Study
Health insurance	2	Two questions about health insurance status; the first asks whether the participant has health insurance; a follow-up question asks if this is their own or their partner's plan [Interview]	• Covariate	Developed for the CHLEW Couples Study

Demographic	Number of items	Description of measure and method of administration	Role in study	Development and modifications
Geographic location	1	In open country but not on a farm, on a farm, in a small city or town, in a medium-size city, in a suburb near a large city, or a large city [Interview]	• Covariate	From previous CHLEW waves
Employment status	1	Working full-time for pay, working part-time for pay, unemployed and looking for work, managing the household, not looking for work, retired or disabled, not looking for work, for other reasons [Interview]	• Covariate	From previous CHLEW waves
Number of children in the household	2	How many children younger than 18 years live in the household; then how many children older than 18 years live in the household. [on the web]	• Covariate	From previous CHLEW waves

[a]IV: independent variable.

[b]FTM: female-to-male.

[c]CHLEW: Chicago Health and Life Experiences of Women.

[d]GED: General Educational Development.

Table 2. Description of major measures.

Scale	Number of items	Timeframe and method of administration	Role in study	Development and modifications
IPA[a]				
CTS[b]; perpetration and victimization	22	Past 12 months [interview]	• DV[c]	• Adapted from Straus [65] • Omitted verbal abuse items because of lack of sensitivity (verbal abuse is assessed using the Psychological Maltreatment of Women scale) • Questions ask both about participant's experiences of victimization and perpetration. • Added questions after each section of the CTS about how often the participant and partner were each drinking
Psychological Maltreatment of Women Inventory perpetration and victimization	30	Past 12 months [interview]	• DV	• Adapted from Tolman [66] • Made pronouns gender neutral • Added parallel questions about participants' perpetration of psychological maltreatment • Added questions about how often the participant and partner were each drinking at each IPA episode
Alcohol use and hazardous drinking				
Drinking consequences	16	Past 12 months [interview]	• Moderator	• Adapted from Wilsnack et al [67] • Modified from the NSHLEW[d] and previous waves of CHLEW[e]; removed four questions that were not germane to the study aims
Help-seeking for alcohol use	1	Past 12 months [interview]	• Moderator	• Adapted from Wilsnack et al [67]
Hazardous drinking (participant's own drinking)				
Heavy drinking	2	Past 30 days and past 12 months [interview]	• Moderator or mediator	• On the basis of guidelines from the NIAAA[f] [68]
HED[g]	2	Past 30 days and past 12 months [interview]	• Moderator or mediator	• On the basis of NIAAA guidelines and relevant research [67,69-71]
Intoxication	1	Past 12 months [interview]	• Moderator or mediator	• On the basis of measures used in the NSHLEW [67] and in previous waves of the CHLEW; see also, Brunborg and Østhus [72]
Maximum quantity drinking	1	Past 12 months [interview]	• Moderator or mediator	• From the national alcohol survey [61]
AUD[h]	11	Past 12 months [interview]	• Moderator or mediator	• On the basis of DSM-5[i] criteria for alcohol use disorder [73]
Hazardous drinking (participant's report of partner's drinking)				
Heavy drinking	2	Past 30 days and past 12 months [interview]	• Moderator or mediator	• On the basis of guidelines from the NIAAA [68]
HED	2	Past 30 days and past 12 months [interview]	• Moderator or mediator	• On the basis of NIAAA guidelines and relevant research [67,69-71]

Scale	Number of items	Timeframe and method of administration	Role in study	Development and modifications
Smoking and other substance use				
Smoking				
Cigarette smoking (yes or no)	1	Current [web-based]	• Moderator	• From previous CHLEW waves
Change in smoking behavior from 12 months ago	1	Current [web-based]	• Moderator	• From previous CHLEW waves
E-cigarette smoking (frequency)	1	Past 12 months [web-based]	• Moderator	• From previous CHLEW waves
Vaping (yes or no)	1	Lifetime [web-based]	• Moderator	• From National Survey on Drug Use and Health [74]
Other substance use				
Substance use (sedatives, painkillers, marijuana, cocaine, stimulants, club drugs, hallucinogens, inhalants, heroin, or other; two questions about help-seeking)	12	Past 12 months [web-based]	• Moderator or mediator	• From the NESARC[j] III [75] • Replaced dichotomous yes or no responses with frequency scale consistent with the NESARC (never, monthly or less often, weekly, daily, or almost daily)
DAST[k]-10	9	Past 12 months [web-based]	• Moderator or mediator	• Adapted from Skinner [76] and Yudko et al [77] • DAST questions were asked if any of the NESARC items above were endorsed. • The first item, which screens for any drug use, was redundant with the NESARC measures; it was omitted.
Minority stressors				

Scale	Number of items	Timeframe and method of administration	Role in study	Development and modifications
Couple-level minority stressors	38	Life right now or past 12 months [interview and web-based]	• IV[l] • Moderator or mediator	• Adapted from Neilands et al [78]; used four subscales (of eight) that are most relevant to study aims: • Couple-level expectations of rejection • Couple-level discrimination • Lack of integration with families of origin • Lack of social support for couples
Sexual identity disclosure	6	Current [interview]	• IV • Moderator or mediator	• Adapted from Herek [79] and used in previous waves of CHLEW
Discrimination scale	12	Past 12 months [interview]	• IV • Moderator or mediator	• Items are based on the Experiences of Discrimination Scale. [80]. These were developed from the AUDADIS-IV[m] study [81] and used in the NESARC-I [82]. • Response options were amended to include additional reasons for discrimination; we ask separately about sex and gender.
Family members' reactions to disclosure	9	Lifetime [interview]	• IV • Moderator or mediator	• Developed for CHLEW Study
Internalized stigma	13	Current [web-based]	• IV • Moderator or mediator	• Adapted from the Lesbian Internalized Homophobia Scale [83]
Stigma consciousness	10	Current [interview]	• IV • Moderator or mediator	• Adapted from Pinel [84] • Items related to stigma related to being a lesbian • Modified to create a bisexual version
Mental and physical health				

Scale	Number of items	Timeframe and method of administration	Role in study	Development and modifications
Adverse childhood experiences (physical and sexual abuse and neglect)	8	Before age 18 [interview]	• Moderator	• From NESARC-III [85,86]
Early Trauma Inventory	5	Before age 18 [interview]	• Moderator	• Adapted from Bremner et al [87] • Psychological abuse subscale only
Characteristics of childhood sexual abuse [88,89]	2	Before age 18 [interview]	• Moderator	• Adapted from Wyatt [88] and Wilsnack et al [89] and used in the NSHLEW and CHLEW
Center for Epidemiological Studies Depression Scale	10	Past week [web-based]	• Moderator or mediator	• No modifications [90,91]
Suicide ideation and attempts	3	Past year [interview]	• Moderator	• Adapted the diagnostic interview schedule: major depression [92]
GAD^{n}-7	7	Past 2 weeks [interview]	• Moderator or mediator	• No modifications [93]
Self-rated physical health [94]	2	Past 30 days [interview]	• Covariate	• No modifications [94]
Self-rated mental health [94]	1	Past 30 days [interview]	• Covariate	• No modifications [94]
Therapy or treatment seeking	5	Past year [interview]	• Moderator	• Used in previous waves of CHLEW
Impact of COVID-19				
COVID-19 diagnosis or symptoms	1	Since the beginning of the COVID-19 pandemic [interview]	• Covariate • Moderator	• Developed for the CHLEW Couples Study
Change to employment situation due to COVID-19	1	Since the beginning of the COVID-19 pandemic [interview]	• Covariate • Moderator or mediator	• Developed for the CHLEW Couples Study
Loss of health insurance due to COVID-19	1	Since the beginning of the COVID-19 pandemic [interview]	• Covariate • Moderator	• Developed for the CHLEW Couples Study
Change in alcohol consumption during COVID-19 pandemic	3	Since the beginning of the COVID-19 pandemic [web-based]	• Covariate • Moderator or mediator	• Developed for the CHLEW Couples Study
Relationship characteristics				
Couple satisfaction index	4	Current [interview]	• Mediator	• Adapted from Funk and Rogge [95] • Removed the question about happiness
Social support, stress, and coping				

Scale	Number of items	Timeframe and method of administration	Role in study	Development and modifications
Abbreviated brief COPE[o] scale	26	Current or in general [web-based]	• Mediator	• Adapted from Carver [96] • Removed venting items (items 9 and 21) • Removed planning items (items 14 and 25) • Removed humor items (items 18 and 28) • Removed acceptance (items 20 and 24) • Removed religion items (items 22 and 27)
Brief resilience scale	6	In general [web-based]	• Moderator or mediator	• No modifications [97]
Drinking Motives Questionnaire	5	In general [web-based]	• Mediator	• Adapted from Cooper [98] • Coping subscale only
LGB[p] positive identity	5	In general [web-based]	• IV • Moderator or mediator	• Adapted from Riggle et al [99] • Community subscale only
Multidimensional Scale of Perceived Social Support	12	Current [interview]	• Moderator or mediator	• Adapted from Zimet et al [100] • Added follow-up asking whether responses to questions about family in the MSPSS[q] referred to the participants' family of origin, partner or children, or family of choice
Perceived Stress Scale	4	Past month [web-based]	• Moderator or mediator	• No modifications [101]
Anger, hostility, emotion regulation, negative affect				

Scale	Number of items	Timeframe and method of administration	Role in study	Development and modifications
BAQ[r]	12	In general [interview]	• Mediator	• No modifications [102,103]
DERS[s]	12	In general [interview]	• Mediator	• Adapted from Kaufman et al [104] • Removed two subscales (awareness and clarity)
DAR[t]	5	In general [interview]	• Mediator	• No modifications [105]
PANAS–SF[u]	10	In general [web-based]	• Mediator	• No modifications [106]

[a]IPA: intimate partner aggression.
[b]CTS: Conflict Tactics Scale.
[c]DV: dependent variable.
[d]NSHLEW: National Study of Health and Life Experiences of Women.
[e]CHLEW: Chicago Health and Life Experiences of Women.
[f]NIAAA: National Institute on Alcohol Abuse and Alcoholism.
[g]HED: heavy episodic drinking.
[h]AUD: alcohol use disorder.
[i]DSM-5: Diagnostic and Statistical Manual-5.
[j]NESARC: National Epidemiologic Survey of Alcohol and Related Conditions.
[k]DAST: Drug Abuse Screening Test.
[l]IV: independent variable.
[m]AUDADIS-IV: Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV.
[n]GAD: generalized anxiety disorder.
[o]COPE: Coping Orientation to Problems Experienced Inventory.
[p]LGB: lesbian, gay, bisexual.
[q]MSPSS: Multidimensional Scale of Perceived Social Support.
[r]BAQ: Brief Aggression Questionnaire.
[s]DERS: Difficulties in Emotion Regulation Scale.
[t]DAR: dDimensions of Anger Reaction.
[u]PANAS–SF: Positive and Negative Affect Scale – Short Form.

Study Instrument and Measures

The demographic measures for this study are included in Table 1. The baseline CHLEW instrument was adapted from the National Study of Health and Life Experiences of Women, which used measures with established reliability and validity. In addition to retaining hazardous drinking, sociodemographic, and other key measures from CHLEW's previous surveys, we added measures that address new research questions and hypotheses relevant to the study aims, including measures of couple-level minority stressors. The CHLEW Couples Study survey instrument retained measures of major drinking variables, relationship variables (eg, relationship satisfaction, commitment, conflict, and IPA), as well as risk and protective factors for hazardous drinking (eg, depression, anxiety, resilience, and social support) included in the longitudinal CHLEW study. We also included several new measures. For example, we added questions about the frequency of physical, sexual, psychological, and verbal IPA—both victimization and perpetration—from the Conflict Tactics Scale [65] and the Psychological Maltreatment of Women Inventory [66]. Each of these measures has been used in prior studies that included SMW [20,107,108]. We also added new couple-level variables (eg, perceptions that the relationship is devalued) developed by LeBlanc et al [50,109]. To account for the potential effects of the COVID-19 pandemic, we included a few questions about the impact of the pandemic on participants, and we will include the date of the interview as a covariate to account for the timing of the interview and at what stage in the pandemic the interview occurred. Table 2 summarizes the measures of the major variables in this study.

Data Analysis Plan

Most measures in the CHLEW Couples Study have established reliability and validity. Nevertheless, we will examine dimensional consistency and internal reliability of all scales and functioning across subgroups. We will correct outliers, data entry errors, or other logical inconsistencies. Given that we used a modified version of respondent-driven sampling to recruit the supplemental sample in CHLEW wave 3 [58], we will adjust for potential interdependence by including a sample cluster corresponding to the seed or referral chain (n=75 chains exist in our data) through which each supplemental sample participant was recruited. We will control for individual-level variables such as age, education, sexual identity, gender, race or ethnicity, education, date of interview, and other variables as appropriate in all APIMs. We may also control for couple-level variables such as relationship length, relationship status (eg, legally

married), whether there are children aged <18 years living at home, and income. The choice of covariates will depend on the specific hypotheses being tested and will be guided by the current literature.

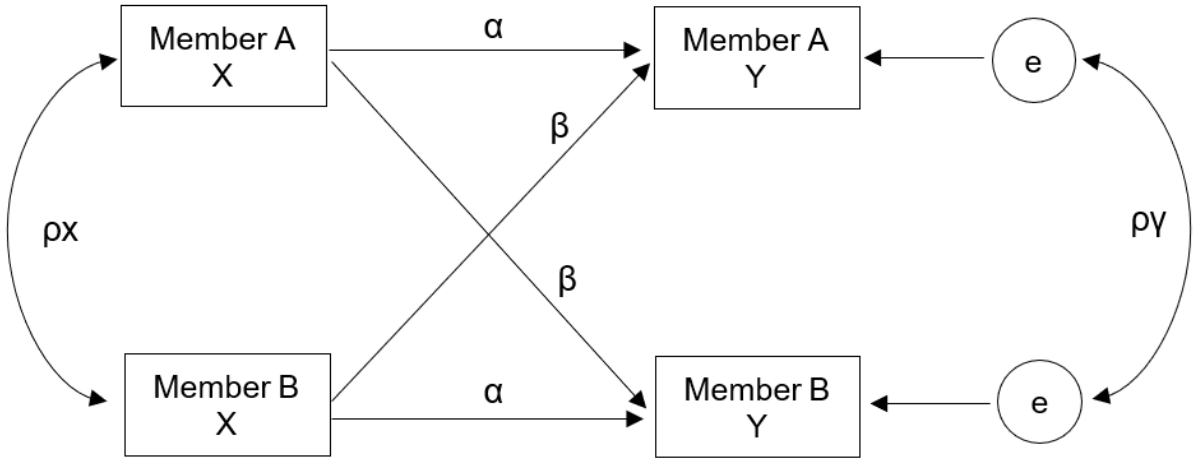
Overview of APIMs

Overview

Analyses for each of the three aims will take full advantage of the dyadic data structure, where information is available on the same variables from each partner of the couple. Using APIM—a framework for analyzing interdependent dyadic data—IPA will be modeled as a function of both actor and partner experiences of their relationship and minority stress. APIM will also permit consideration of other potentially important factors influencing each partner's IPA perpetration and victimization, such as actor and partner discrepant drinking patterns or discordant experiences of minority stress.

We will implement APIMs at various levels of complexity to estimate the effects. As the sample will include predominantly same-sex partners, this results in the so-called indistinguishable dyads (who is labeled member A vs and who is labeled member B in the couple does not make a difference). All analyses will use APIM models constrained for indistinguishable dyads, regardless of whether the couple is same-sex or gender or mixed-sex or gender. That is, we will include all couples in the same indistinguishable dyad model (regardless of their sex or gender; we expect that <10% of couples will be mixed-sex or gender). Dyadic distinguishability (and the associated distinguishable model) refers to whether the two individuals within a dyad possess a distinctive characteristic that differentiates them in a manner relevant to the primary research question [110]. We will not elevate sex or gender as a distinguishable variable in the dyadic sense but instead, consider it a person-level covariate. Hence, we will use standard constraints within the APIMs such that actor effects will be fixed to be the same across participants, as will partner effects. In the basic APIM (Figure 3), α represents the extent to which the independent variable X of a participant influences their own score on the dependent variable Y (actor effect), and β represents the effect of the independent variable X of a participant on their partner's dependent variable Y (partner effect). In addition, we will obtain the intraclass correlation for the independent variable X, which is *p*x, and the intraclass correlation of Y after accounting for X, which is *p*y. Implementation of the APIM is available within the structural equation model framework in Mplus (Muthén and Muthén). We will control for individual-level variables such as age, education, sexual identity, race or ethnicity, length of relationship, and other variables as appropriate in all APIMs.

Figure 3. Basic actor-partner interdependence models for indistinguishable dyads.



Aim 1

Although no studies have examined associations among minority stress, hazardous drinking, and IPA within a dyadic framework yet, we will examine a number of hypotheses derived from nondyadic research. We will use individual measures of minority stress as independent variables to predict each hazardous drinking outcome separately and then each IPA outcome (each partner's reports of perpetration and victimization) separately. We will also fit models with each measure of hazardous drinking, predicting each measure of IPA. These effects represent the total (unmediated) effects of each variable on the other; they will show which measures are more or less strongly associated with one another, as well as which exhibit significant actor or partner effects. Additional models will test for differential effects by sexual identity, race or ethnicity, and longer- versus shorter-term relationships. These differential effects will be tested by including an interaction between X and each potential moderator in the APIM.

Aim 2

We will expand the APIMs tested in aim 1 to include multiple predictor variables, with some as mediators; we will also include interaction terms with potential moderating variables [111]. For example, to be a mediator of the relationship between minority stress and IPA, a variable M (eg, relationship satisfaction) must (1) exhibit a significant association with minority stress and (2) either show a significant association with the IPA outcome

variable or, based on counterfactual theory, show a significant interactive effect with minority stress on the IPA outcome (each partner's reports of perpetration and victimization). To test (1), we will fit the model in Figure 3 with the mediator as the outcome variable and test actor and partner effects (ie, the effect of minority stress on the mediator). Then, for (2), we will test the mediator—relationship satisfaction—as a predictor of IPA while also including minority stress in the model. We will use the bootstrap method to obtain standard errors and test the statistical significance of the mediation effect derived under the counterfactual framework, which allows for a possible interactive effect between relationship satisfaction and minority stress. We note that this inclusion of interactions in mediation effects goes beyond what is traditionally presented for mediation, for example, in Ledermann et al [111]; however, it is quickly being considered best practice and is implementable in Mplus [111-113]. Within the structural equation model framework, we can estimate these effects in a single integrated model, which allows us to estimate the mediation effect of actor or partner simultaneously. For example (*mediation hypothesis*): associations between minority stress (individual- and couple-level) and IPA will be mediated by each partner's satisfaction with the relationship. Discrepancies in satisfaction will be associated with hazardous drinking in both partners, which in turn will be associated with IPA. Examples of *moderation hypotheses* are that hazardous drinking will moderate (ie, strengthen) the effects of minority stress and relationship dissatisfaction on IPA, and associations between minority stress (individual- or couple-level) and hazardous drinking or IPA will be moderated by each partner's history of childhood abuse.

Aim 3

This aim is guided by the I^3 theoretical perspective. We will address this using APIMs that include the effects of instigating factors (eg, relationship conflict), impelling factors (eg, minority stress, negative affect, and trait anger), and inhibiting factors (eg, relationship length or level of commitment and emotion regulation) or disinhibiting (eg, hazardous drinking) on IPA perpetration. We will operationalize IPA perpetration to be present for a member of the couple if either that participant reports perpetrating or their partner reports experiencing (ie, victimization) IPA. It is a well-established finding that intimate couples' agreement on the occurrence of IPA is low to moderate [114]. Given social desirability concerns about reporting IPA, couple reports have been used in the large majority of dyadic IPA studies (based on the assumption that couple members are more likely to deny an actual occurrence than to falsely report IPA). Conceptually, the I^3 perspective requires certain combinations of variables within both the actor and partner and across the 3 domains (instigating, impelling, and inhibiting) to be present if the risk of IPA perpetration is strong. Hence, we will include interactive effects (cross-products) between actor and partner predictor variables (eg, partner A's hazardous drinking with partner B's negative affect) within the APIM. The model will also include actor and partner interactions on the same variables corresponding to concordance (both partners drink heavily, neither partner drinks heavily, etc) and discordance. Tests of the significance of these different interactions will provide the necessary information for each step of the I^3 model. An *example hypothesis* is that partner A's hazardous drinking and partner B's negative affect will interact to predict partner A's IPA perpetration.

Given our planned sample size of 302 dyads (604 individuals), with two-sided tests and α=.05, we will have >80% power to detect small associations (ie, standardized regression coefficients as small as 0.12) in the full sample. Although not central to the study aims described above, we plan to examine demographic differences in the associations between hazardous drinking and IPA. On the basis of the racial/ethnic and sexual identities of CHLEW participants and assuming that most partners will have similar characteristics, our sample will include approximately 221 Black and 143 Latinx SMW and 206 bisexual women. The anticipated sample size will provide good power (>80%) to detect small-sized associations (ie, standardized regression coefficients as small as 0.20 in bisexual and Black and 0.23 in Latinx participants) in each subgroup. These detectible effect sizes apply to all the direct effect estimates of interest in aims 1, 2, and 3 [115,116]. The power to detect interactive effects is driven primarily by the sample size in the smallest cells of the interaction. We also have acceptable power to detect such interactions. For example, if the effect size of minority stress on heavy drinking for lesbian women is 0.20 and the effect for bisexual women is 0.40, we will be able to detect with 80% power that these effects are different (ie, significant minority stress × sexual identity interaction). Moreover, bisexual women and SMW of color are more likely than lesbian and non-Hispanic White women to report heavy drinking or drinking-related problems and IPA, increasing the likelihood of detecting significant race/ethnicity by sexual identity interactions [7,8,16,117-120]. On successful completion, this study will be the largest couple cohort study of its kind. The large sample size and large subgroup sizes will provide good power to detect clinically and practically meaningful effects.

Results

Data collection for this project began in February 2021 and will continue through 2023. Preliminary data are expected to be available in mid-2024.

Discussion

Principal Findings

The changing social landscape, including the legalization of same-sex marriage, has led to heightened interest in research on same-sex relationships; however, this topic is substantially underrepresented in the literature. Furthermore, although research on alcohol use and IPA among sexual minority people has grown in the past 2 to 3 decades, important gaps remain, which the CHLEW Couples Study will address. First, most research on SMW has focused on the prevalence of IPA rather than on individual, relational, and contextual factors. Second, existing studies have focused predominantly on the main effect of associations between hazardous drinking and IPA. Less examined and understood are potential mediators and moderators of these associations, which are particularly important in

informing interventions. Third, there are very few published studies on the association between hazardous drinking and IPA among SMW that have included both partners, and even fewer have examined both victimization and perpetration. Addressing these gaps represents an important shift from our (and others') predominant focus on individual risk factors to also considering couple-level factors. Finally, sample sizes of sexual minority people in population-based studies are typically small, and subsamples of those who are both sexual and racial or ethnic minorities are even smaller; consequently, research on subgroups (eg, racial or ethnic minority SMW) is very rare.

This study is guided by minority stress and IPA theoretical perspectives to better understand both individual and dyadic factors that promote or deter hazardous drinking and IPA among SMW and their intimate partners. Building on our previous work that examined the impact of hazardous drinking on general and sexual minority–specific stressors that accumulate throughout the life span, we will capitalize on an opportunity to examine the links among minority stress, hazardous drinking, and IPA. This study also has a more balanced perspective that considers both risk and resilience from the perspectives of both members of the couple. We hope to advance the fields of sexual minority health and women's health. Specifically, we will add significantly to the currently sparse knowledge about individual, interpersonal, relational, and contextual factors that contribute to elevated rates of physical and mental health problems among SMW.

Limitations and How They Will Be Addressed

In addition to the strengths outlined above, we recognize the limitations of the study. First, it is possible that some study participants may be reluctant to share information about IPA in their relationship because of feared loss of confidentiality or social desirability. These fears may be complicated by the COVID-19 pandemic, given that couples who live together may have less privacy because of shelter-at-home guidelines. For purposes of confidentiality, partners will be interviewed by separate interviewers and assured that no information they provide will be shared with their partners and that all data will be treated as confidential. We will provide all participants with earbuds (with microphones) to help protect privacy (ie, so that others in the household cannot hear the questions being asked of the participant). We will employ interviewers experienced in conducting interviews that ask questions about sensitive topics and will provide them with extensive training on how to ensure participant privacy and maintain confidentiality. To reduce social desirability bias, we will preface IPA questions with a brief introduction that contains additional confidentiality assurances [121-123]. Also, to address the possibility of underreporting of IPA by one or both members of a couple, we will compare their reports of IPA perpetration and victimization. We will consider IPA to have occurred if either partner reports having perpetrated or experienced a particular form of IPA. We will conduct additional analyses of cases in which partners provide discrepant reports of perpetration or experience of IPA to gain additional insights about each partner's experiences. We will also examine variables such as hazardous drinking, that may be associated with discrepancies in partner perceptions of IPA.

Second, we expect to have a small number of partners who are men or report transgender or nonbinary gender identity. We will conduct exploratory analyses to glean information about potential similarities and differences in findings based on the sex or gender of partners. As we will not know how many mixed-gender dyads we will have in our final sample until the recruitment is over, it is unclear whether we will have large enough subsample sizes of, for example, transgender partners or cisgender men partners to examine couple-level gender differences. There is very little research on couples among whom at least one member is transgender; however, there is some suggestion in the literature that alcohol use may be influenced by unique aspects of those relationships [124-126]. There is also little research with SMW in relationships with cisgender men; however, available data suggest that partner gender plays a key role in drinking-related behaviors in these couples [127-129].

Third, our past experiences of scheduling interviews with individual CHLEW participants suggest that it will take more time and effort to schedule both the CHLEW participant and their partner's interview within close proximity (the same week). As it is important that the same periods be reflected in reports from each member of the couple, we will provide a US $20 incentive to each member of the couple who is willing to be interviewed in the same week (in separate, private locations). As we will train at least 5 interviewers and because research staff will also conduct interviews, we can be flexible and accommodate most schedule requests. Finally, the CHLEW Couples Study uses a cross-sectional design. For this reason, inferences about causal relationships will be considered cautiously, with careful attention to assumptions about causal ordering that cannot be directly tested.

Implications for Intervention

We expect that the findings of this study will provide the basis for future research aimed at clarifying the causal pathways linking hazardous drinking and IPA among SMW. This research can support the development of individual and dyadic prevention and intervention strategies for SMW and their partners. Research with heterosexual couples suggests that relationship factors are especially important to consider in intervention development [130-132]. Given the existing empirical evidence, there is reason to believe that dyadic interventions are particularly well-suited for treating IPA, especially among couples who do not wish to separate. We are particularly interested in gaining information about modifiable targets for intervention—both general (eg, couple communication, alcohol use behaviors, and emotion regulation) and sexual minority–specific (eg, conflicts about differing levels of sexual identity disclosure)—that can be used in working with SMW. For example, if we find that rejection from families of origin is a particularly strong modifier of the link between minority stress and IPA among couples in the study, dyadic interventions that aim to help couples cope with familial rejection and find other sources of support could be tested.

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Conflicts of Interest

None declared.

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Abbreviations

APIM: actor-partner interdependence models
CHLEW: Chicago Health and Life Experiences of Women
I^3: I-cubed
IPA: intimate partner aggression
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIH: National Institutes of Health
SMW: sexual minority women

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Protocol

Psychological Impact of the COVID-19 Pandemic and Social Determinants on the Portuguese Population: Protocol for a Web-Based Cross-sectional Study

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Abstract

Background: The COVID-19 outbreak and consequent physical distance measures implemented worldwide have caused significant stress, anxiety, and mental health implications among the general population. Unemployment, working from home, and day-to-day changes may lead to a greater risk of poor mental health outcomes.

Objective: This paper describes the protocol for a web-based cross-sectional study that aims to address the impact of the COVID-19 pandemic on mental health.

Methods: Individuals from the general population aged 18 years or more and living in Portugal were included in this study. Data collection took place between November 10, 2020, and February 10, 2021. An exponential, nondiscriminative, snowball sampling method was applied to recruit participants. A web-based survey was developed and shared on social media platforms (eg, Facebook, Instagram, Twitter, LinkedIn, and WhatsApp groups) and through e-mail lists for recruitment of the seeds.

Results: Data analysis will be performed in accordance with the different variables and outcomes of interest by using quantitative methods, qualitative methods, or mixed methods, as applicable. A total of 929 individuals had completed the web-based survey during the 3-month period; thus, our final sample comprised 929 participants. Results of the survey will be disseminated in national and international scientific journals in 2021-2022.

Conclusions: We believe that the findings of this study will have broad implications for understanding the psychological impact of the COVID-19 pandemic on Portuguese residents, as well as aspects related to the informal economy. We also hope that the findings of this study are able to provide insights and guidelines for the Portuguese government to implement action. Finally, we expect this protocol to provide a roadmap for other countries and researchers that would like to implement a similar questionnaire considering the related conclusions.

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KEYWORDS

COVID-19; public health; mental health; study protocol; psychological impact; anxiety; depression; grief; behavior change

Introduction

Background

Mental health is an integral and essential component of health. It constitutes a relevant and increasing burden of disease worldwide [1], with major depression expected to be the largest contributor by 2030 [2]. Thus, mental health is extremely important, not only due to its own value for living but also because it is a critical determinant of physical health [3].

Nevertheless, mental health represents a complex public health challenge wherein environmental factors play a fundamental role. In particular, the relationship between viral illnesses and mental health conditions, especially anxiety and depression, have long been studied. Previous studies on epidemics, such as influenza [4,5], varicella-zoster [6,7], herpes simplex, HIV/AIDS, and hepatitis C [8-11], have already described the strong links between infectious diseases and mental health outcomes.

Pandemic disasters have been part of the human history for centuries, and the human response to the COVID-19 pandemic inevitably differs from that toward other disasters, as social gatherings are being discouraged. Instead, the exact opposite—separation, isolation and quarantine—is required to manage the outbreaks [12]. Although such disease containment measures may suppress the outbreaks, they have the unintended consequences of constraining family rituals, norms, and values, which regulate and protect family functioning in times of crisis [13]. The COVID-19 pandemic and the resulting physical distancing measures implemented by many countries caused disruptions to daily routines that may have a strong impact on mental health.

In a recent Kaiser Family Foundation Health tracking poll, nearly half of adults in the United States reported that their mental health has been negatively impacted due to worry and stress over the outbreak [14]. Although necessary to prevent loss of life due to COVID-19, public health measures expose many people to situations that may be linked to psychosocial problems, such as isolation and unemployment. Additionally, anxiety and depression are increasingly common [13], as people are fearful of themselves or their loved ones falling ill, and they are uncertain of the repercussions of the pandemic, which may be linked to a greater vulnerability toward the virus [13].

Over the last 20 years, other outbreaks of infectious diseases have occurred worldwide. The most recent examples include the outbreak of severe acute respiratory syndrome (SARS) in 2002 [15] and the 2009-2010 influenza A/H1N1 influenza pandemic [16]. Profound psychosocial implications at the individual, community, and international levels have been documented in the past epidemics and pandemics [17]. However, the world has not experienced an epidemic or pandemic with the same intensity and duration as that of COVID-19 in recent times.

Therefore, the COVID-19 pandemic may have serious implications for individual and collective health, as well as emotional and social functioning in the present and future. According to a 2020 review conducted by Brooks et al [18], being forced to stay at home leads to negative psychological effects such as fear, frustration, and anger. The negative impact of confinement can have long-lasting effects on an individual. Further understanding of the biopsychosocial consequences of pandemic disasters, such as COVID-19, is the first step toward achieving best practices on global, regional, and local preparedness and response [19]. In order to understand the consequences of the COVID-19 pandemic on people's mental health, we have two main aims under the construct of this protocol: The first aim is to explore the mental health status of the general adult population during the COVID-19 outbreak, in terms of psychological impact caused by the pandemic and resulting anxiety and depression symptoms. The second aim is to examine the extent to which different sociodemographic and other variables are associated with psychological impact, anxiety, and depression.

We believe there is an urgent need to broaden our knowledge about mental health in the Portuguese population as a first step to develop psychological interventions, so that the lasting psychological negative consequences of the pandemic can be reduced. To address this gap in the literature, this article presents the study protocol for a survey on the psychological impact the COVID-19 crisis has had on the psychological health of the Portuguese population.

Objectives and Aims

The overall objective of this cross-sectional study is to evaluate the impact of the COVID-19 pandemic on the mental health of individuals residing in Portugal. This study is of particular importance due to the possible psychosocial impact of the COVID-19 pandemic and associated confinement measures on the mental health of individuals, as well as to examine associated socioenvironmental determinants. In particular, our research will attempt to verify and measure whether the following issues are interconnected: (1) employment status during the COVID-19 pandemic; (2) the psychological impact of online education at home on children, adolescents, and parents; (3) household food insecurity; (4) the impact of having a confirmed COVID-19 diagnosis on the individual's mental health; (5) anxiety and depression in relation with employment status and confinement measures; (6) understanding how the pandemic may cause changes in the experiences of loss and grief; and finally, (7) domestic violence during the lockdown.

Most studies published since the beginning of the COVID-19 pandemic have focused on a set of social and mental health determinants directly related to the pandemic, in addition to epidemiological data associated with the infection. Thus, the choice of the determinants presented above is related to the important documentation and evidence that has been published in recent months, namely on the issues of unemployment due to lockdown and restrictive measures [20,21]; working from home along with children participating in online education from home [22]; food insecurity [23,24]; and the impact of the COVID-19 pandemic on mental health [25], anxiety and depression [26-28], grief [29-31], and domestic violence [32-34].

The proposed project is grounded on the importance of mapping the most relevant psychosocial mental health determinants during the COVID-19 pandemic among Portuguese residents.

We expect to provide evidence based-knowledge to guide policy-level practices directly towards the reduction of health inequities, increased access to psychological services, and also raise awareness for negative mental health outcomes as a result of job loss, changes in routine, loss of someone close, and food insecurity.

The specific research aims outlined below will help us gather data for the study, including data from all subregions of the country. We aim to analyze the unique patterns of the impact of the COVID-19 pandemic through the use of a web-based survey applied to a nonprobabilistic sample of adult Portuguese residents.

Aim 1

We aim to analyze possible changes in employment status since the beginning of the pandemic, taking into consideration at least age, gender, occupation, and education as potential confounders. Questions on occupation before and since the beginning of the pandemic, changes in income, and pandemic-related unemployment will also be asked to fully access possible significant associations.

Aim 2

We aim to understand how parents and/or caregivers at home have changed their normal routines due to web-based education and working from home, and to examine the possible existing association with stress and anxiety disorders. Additionally, we will evaluate the increase in the use of anxiolytics, as reported by the National Authority for Medication and Health Products (Infarmed in Portuguese) [35].

Aim 3

We aim to assess the prevalence of household food insecurity among the Portuguese population since the beginning of the COVID-19 pandemic. Food security status will be evaluated using the US Household Food Security Survey Module: Six-Item Short Form [36,37]. Participants will be asked about the food eaten in their households, in the previous 12 months, and whether they were able to afford the food they need. We will also include an option for open text for participants to comment on their experiences and perceptions of food insecurity changes since the beginning of the COVID-19 pandemic in order to support their answers.

Aim 4

We aim to analyze increase in anxiety and depression in levels relation with COVID-19 pandemic. Anxiety and depression symptoms will be evaluated using the Hospital Anxiety and Depression Scale (HADS) [38,39], which indicates how an individual has felt in the past week. Mental health conditions, such as anxiety and depression, can affect an individual´s thought process, feelings, mood, and behavior in such a way that they can influence the individual's ability to relate to others and to complete everyday tasks. Since these conditions can be situational—short-term or long lasting, chronic—we want to assess and understand how the COVID-19 pandemic may influence mental status.

Aim 5

We aim to evaluate prolonged grief disorder since the beginning of the COVID-19 pandemic. For this purpose, we will use the PG-13 Prolonged Grief Disorder as an instrument to collect and analyze data. The following criteria must be met for prolonged grief disorder to be considered: "the experience of loss-generating intense longing and yearning for the deceased must extend for at least six months" [40,41]. Based on these criteria and the fact that the first case of COVID-19 in Portugal was on March 2, 2020, and that our questionnaire was launched on November 10, 2020, those participants that did not meet these criteria will be excluded from this part of the analysis.

Besides facing arduous conditions over the last days of life due to COVID-19 protection measures, these criteria also created a challenging post-death scenario, since funerals and burials were postponed or held remotely [42,43]. Accordingly, the presence of family members and loved ones during such crucial moments became impossible. Therefore, the impact of these circumstances on the mental health of family members, as well as the anxiety and stress experienced, must be carefully examined and understood.

Aim 6

We aim to evaluate domestic violence between couples before and since the beginning of the COVID-19 pandemic. For this purpose, we will use an adaptation of the screening questions proposed by the Portuguese Association for Victim Support [44].

Sociodemographic characteristics were collected at the beginning of the survey and all of the measuring instruments indicated above have been previously validated for the Portuguese population.

Methods

Design

The study design can be characterized as a web-based cross-sectional survey and is based on the construct of the snowball sampling method. Snowball sampling began as a method for sampling networks. Coleman was a pioneer in using this technique as a method for studying a person's social environment [45]. Later, Goodman and Kish presented a more rigorous version of the method using a probability sample [46].

The snowball sampling can be defined as "[A] technique for finding research subjects. One subject gives the researcher the name of another subject, who in turn provides the name of a third, and so on. This strategy can be viewed as a response to overcoming the problems associated with sampling concealed hard to reach populations such as the criminal and the isolated" [47]. In our study, a virtual snowball sampling survey was disseminated first through social networking channels, namely Facebook, Instagram, LinkedIn, WhatsApp groups, and Twitter, and then by using the personal mailing lists of the researchers involved.

The selection of this method for the dissemination of the questionnaire was based on the convenience of reaching participants from a variety of places, which increases the sample

size and reduces the costs and time associated with data collection. We believe that the use of Facebook, Instagram, Twitter, LinkedIn, and personal mailing lists (all free of charge) to contact individuals can minimize problems associated with "spam" messages, impersonal contact, unclear answers, and low response rates. Moreover, the possibility of having access to *offline contacts* through the recommendation by *online contacts* can reduce problems associated with selection bias and representation.

As Brickman-Bhutta explained, "Facebook and other social network sites allow us to carry chain-referral methods into the age of the Internet, while also exploiting the strengths of online questionnaires" [48].

Therefore, in this study, participants were asked, at the beginning and at the end of the questionnaire, to share the survey with at least five of their personal contacts to ensure that the snowball sampling method was effective.

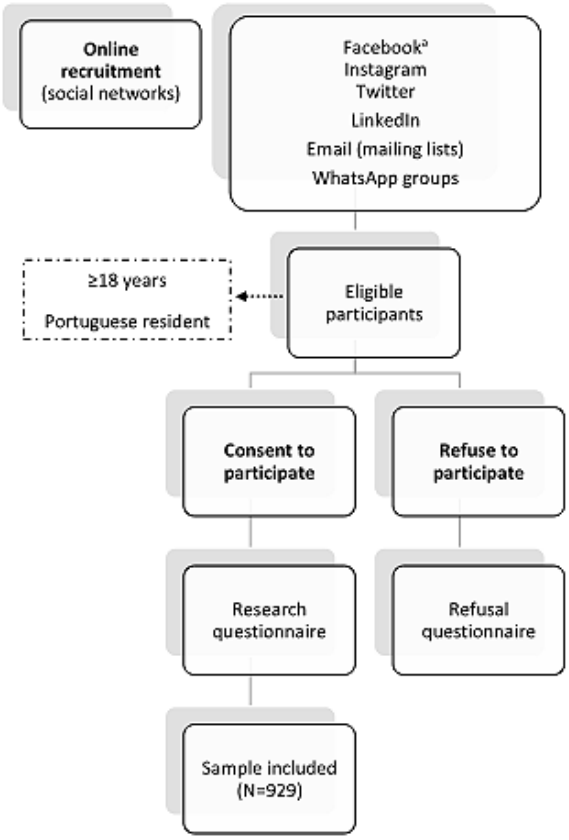
Study Population

Participants from the general population in Portugal were enrolled in this study. The inclusion criteria were as follows: (1) age 18 years or older and (2) a resident of Portugal. Participants not meeting these inclusion criteria were excluded from the study. Participants' birth dates will be recorded as age in years, and those aged under 18 years will be excluded from the analysis. In addition, participants who reported they live outside Portugal were excluded from the final sample.

Study Procedures and Data Collection

Study procedures are illustrated in Figure 1. The enrollment was ongoing for 3 consecutive months from November 10, 2020, to February 10, 2021.

Figure 1. Flowchart of the study procedures and enrollment of participants. ISPUP: Instituto de Saúde Pública, Universidade do Porto.



[a]The questionnaire was shared via Facebook groups, personal accounts, and ISPUP's institutional page

Data collection included general demographic variables, such as age, gender, region, educational level, and marital status. It also included variables related to COVID-19, such as incidence in family. In addition, information on other health-related risk factors such as a history of noncommunicable diseases was collected. To complement and to address our study aims, the survey included the evaluation of the following dimensions: (1) employment status, (2) children and web-based education, (3) food insecurity, (4) SARS-CoV-2 infection and mental health, (5) anxiety and depression, (6) grief and mourning, and (7) domestic violence.

All the instruments used to evaluate anxiety and depression, grief and mourning, and domestic violence have previously been validated for use for the Portuguese population [38,41,44]. Despite the scale used for food insecurity assessment not being fully validated for the Portuguese population, previous studies among Portuguese individuals have reported good internal consistency [49,50].

The questionnaire was administered in Portuguese—the official language of Portugal. A pretest of the questionnaire was conducted with 15 people. We asked these participants to complete the survey the same way that it would be completed in the actual project—that is, by using a web-based tool. We asked them to annotate doubts, questions, and bugs in the web-based questionnaire and possible improvements or clarifications. Thereafter, we took all the comments and improved the questionnaire by clarifying some questions and correcting typographical errors. Moreover, since the scales used to measure food security, anxiety and depression symptoms, prolonged grief disorder, and violence were already translated and validated previously for the Portuguese population, no pre-test on the translation was conducted; this was because the tools used were already reliable and have shown good internal consistency in the validation studies previously conducted.

For the purpose of possible replication of this method, an English-translated version of the questionnaire is provided in Multimedia Appendix 1.

Data Analysis

Data will be analyzed using quantitative methods, qualitative methods, or mixed methods depending on the different variables and outcomes as described above.

Statistical Analysis

Characteristics of participants will be described by absolute and relative frequencies and compared using the Chi-square test or Fisher exact test, as appropriate, in categorical variables. Medians and percentiles (P25-P75) will be used to describe continuous variables compared using the Mann-Whitney *U* test. Unconditional logistic regression models will be computed to assess the associations between the instruments used and sociodemographic variables. Odds ratios and corresponding 95% CIs will be estimated.

Exploratory factor analysis using principal component analysis will be applied to the anxiety and depression scale and the PG-13 instrument. Additionally, the oblique rotation will be performed to examine the factor structure of the scales. Internal consistency of the tools will also be assessed by measuring inter-item correlation and Cronbach coefficient.

Furthermore, poststratification survey weights will be calculated to try to correct oversampled subpopulations (eg, younger, more educated participants) and undersampled subpopulations (eg, older, less educated, and male participants) [51]. Adjusting the weights will increase the stratum variance and, thereby, the design effect. We will compare our survey data with existing census for the country (2011 or 2021 census, that are being currently updated).

Qualitative Data Analysis

Open-ended questions will be analyzed using content analysis. In the present study, and taking into consideration the different objectives presented above, we included open-ended questions in all different sections of the questionnaire to comprehensively explore participants' feelings, constrains, advantages, disadvantages, problems, among other aspects. Unlike a closed-ended question that leaves survey responses limited and narrowed to the given options, open-ended question allows participants to probe deep into their answers, providing valuable information about the subject at hand. The responses to these questions can be used to attain detailed and descriptive information on a topic.

The following open-ended questions were added to the survey: (1) relation with children and school from home, including changes in routine and its positive and/or negative effect on personal and professional life; (2) food security, including worsening of the household situation (eg, less money to buy food due to the COVID-19 pandemic); (3) health care, including the use of anxiolytics and/or antidepressants to explore the reasons behind starting to consume such medicines since the beginning of the COVID-19 pandemic; (4) COVID-19 infection, including the presence of anxiety or depressive symptoms in consequence of a positive diagnosis; (5) mental health, including anxiety and depression symptoms in relation with the pandemic situation; and (6) grief and mourning, including impact of the loss on one's daily life.

Content analysis is a research tool used to determine the presence of certain words, themes, or concepts within qualitative data, such as text. By using content analysis, we will be able to explore the underlying meanings and psychosocial processes of the quantitative data collected. Thus, it will provide additional knowledge and a deeper understanding of the psychological impact of the COVID-19 pandemic [52]. We based the process of coding and analysis on the principles proposed by Braun and Clarke [53], which implied an iterative process of systematically identifying and organizing patterns of meaning (ie, themes) in the data set. An inductive coding framework was applied using a group-up approach where codes were derived from the data. A 4-step approach was performed: (1) first read of the answers and coding, (2) organization of the codes into categories and subcodes, (3) further rounds of codes whenever needed, and (4) turning the codes and categories into the final narrative.

Mixed Methods Analysis

The term "mixed methods" refers to an emergent methodology of research that advances the systematic integration, or "mixing" of quantitative and qualitative data within a single investigation or sustained program of inquiry. The basic premise of this methodology is that such integration permits a more complete and synergistic usage of data than separate quantitative and qualitative data collection and analysis. Mixed methods are especially useful in understanding contradictions between quantitative results and qualitative findings [54].

Considering the above-mentioned explanation, we also aim to use both quantitative and qualitative data, whenever possible. Since our open-ended questions complement some of the quantitative questions, we aim to explain the quantitative data in more detail through the qualitative data, namely data on the psychological and routine changes impact of teleschool and teleworking—the balance between work, parenting, and house care; food security changes concerning, for instance, job loss due to the pandemic and its relation with household income and affordability to buy food; use of anxiolytics and/or antidepressants due to changes in daily life concerning the pandemic—feelings of anxiety and depression; symptoms of

anxiety and depression before and since the beginning of the pandemic; and exacerbated symptoms of grief and mourning due to the pandemic restrictions on proper farewell moments. Thus, the qualitative approach used in this study will only apply to some of the subset aims in order to produce deeper knowledge on the research areas of interest.

Ethics and Informed Consent

Ethical approval was obtained from the Ethics Committee of the Institute of Public Health of the University of Porto (CE20166). All participants, by accessing the questionnaire through the link, were asked to provide informed consent according to the Ethical Principles for Medical Research involving human subjects, expressed in the Declaration of Helsinki and the current national legislation. Since this is a web-based survey, participants could select between two options: accept to participate in the study or decline to participate. For the latter, a refusal questionnaire with questions on gender, age, number of years of education completed, and the reason for not accepting to participate could be answered. The questionnaire is confidential, and no data that would allow for the identification of the participants is collected.

Results

Participant enrollment has now been completed. A total of 929 participants completed the survey. The majority of participants were female (659/929, 70.9%). The mean age of participants was 36.8 (SD 11.5) years; a majority of the participants have a university degree (700/929, 75.3%), and 21.1% (196/929) have at least one comorbidity, and 4.4% (41/929) have had a confirmed COVID-19 diagnosis. Moreover, Sociodemographic characteristics and information on confirmed COVID-19 diagnosis of participants who were included are shown in Table 1. Results of the survey will be disseminated in national and international scientific journals in 2021-2022.

Table 1. Preliminary sociodemographic characteristics and COVID-19 diagnosis of participants enrolled in the study (N=929).

Characteristic	Participants, n (%)
Gender	
Male	265 (28.5)
Female	659 (70.9)
Missing	5 (0.5)
Age, mean (SD)	36.8 (11.5)
Education	
≤12 years	217 (23.9)
University	700 (75.3)
Missing	12 (1.3)
Marital status	
Single	450 (48.4)
Married	405 (43.6)
Divorced	65 (7)
Widowed	5 (0.5)
Missing	3 (0.3)
Parish of residence	
North	590 (63.5)
Centre	98 (10.5)
Alentejo	11 (1.2)
Lisbon Metropolitan Area	186 (20.0)
Algarve	18 (1.9)
Islands (Azores and Madeira)	8 (0.9)
Missing	18 (1.9)
Household size	
1 person	144 (15.5)
2 persons	280 (30.1)
≥3 persons	487 (52.4)
Missing	18 (1.9)
Working status during the COVID-19 pandemic	
Continued employed	655 (70.5)
Become unemployed	73 (7.9)
Continued unemployed	45 (4.8)
Student	48 (5.2)
Housewife	5 (0.5)
Retired	14 (1.5)
Missing	89 (9.6)
History of previously diagnosed diseases	
Yes	196 (21.1)
No	719 (77.4)
Missing	14 (1.5)
Positive COVID-19 diagnosis	
Yes	41 (4.4)

Characteristic	Participants, n (%)
No	878 (94.5)
Missing	10 (1.6)

Discussion

Overview

There are well-established associations between infectious diseases and mental health outcomes that have shown profound psychosocial implications at the individual, community, and international levels. The human response to pandemics such as the COVID-19 discourage social gatherings of people and warrant separation, isolation, and quarantine. Although such disease containment measures may quell the outbreak, they have the unintended consequences of constraining family rituals, norms, job loss, work from home with children to help at the same time, changes in food behaviors, and anxiety and depression.

The uncertainty of how this novel disease will develop together with the unusual situation of being confined at home is most likely leading people to experience negative psychological consequences [18]. Despite the urgent need claimed by several studies [18,55-57] to systematically examine the psychological health of the population being most affected by the COVID-19 pandemic, scientific data on this matter, concerning the Portuguese population, is still scarce. Our proposed study protocol aims to address this gap in the literature, by conducting a survey to evaluate the psychological impact of the COVID-19 crisis on the Portuguese population. Specifically, we collected data on the psychological impact of the COVID-19 crisis on the mental health of adults, including the psychological impact as well as anxiety and depression symptoms.

Findings from this study will provide useful information regarding the impact of the COVID-19 pandemic on mental health. This study will also highlight other health-related risks according to sex, education, employment status, and food security status. It also serves as an important descriptive starting point for future follow-up surveys in specific target groups.

This study will also contribute to developing national and European evidence-informed policies that translate research into effective health strategies, which are sustainable over time. According to socioeconomic dimensions, a comprehensive analysis will also contribute to developing policies that affect equity and human well-being.

Limitations

Some limitations can be anticipated since this study comprises a nonrepresentative sample of the Portuguese population. One of the main limitations of our study is related to selection bias. Selection bias in this sample can be discussed since only specific groups of the population use the internet and social networks, such as Facebook and LinkedIn. Nevertheless, we believe that the sampling method used, despite its limitations, is still very effective and more so nowadays, given the social distancing measures imposed by the governments.

Additionally, we must consider that virtual snowball sampling techniques imply a semirandom selection procedure, which means that we cannot generalize our results for the general population. Nonprobabilistic sampling can disproportionately affect prevalence estimates in our results. Therefore, poststratified weights will be applied to make the sample more representative of the general population. Poststratification relies on the data obtained in the survey itself that were not available before sampling, and it adjusts the weights so that the totals of each group are equal to the known population total. Nevertheless, this study protocol and its preliminary results have described an efficient method that has the capability of extending the sample size, improving response rate, and recruitment effectiveness.

Strengths

We consider that the structure of web-based questionnaires can reduce the possibility of errors because (1) it is possible to program specific instructions for each question (eg, multiple answer options, one answer only, open-ended questions, Likert scales); (2) the answers are easily visible when displayed on computers or smartphones; and (3) automatic filters can be applied for the questions, according to the respondents' answers. Moreover, another strength of the study is the open-ended questions that permit the respondent to have the liberty to include details about their feelings, attitudes, and views that they usually would not be able to submit via responses to close-ended questions. Allowing the respondents to answer in their own words can lead to empowering outcomes. By using open-ended questions, participants are able to express and articulate opinions that may be extreme, unusual, or simply ones that the researcher did not think about when creating the survey. This often provides researchers rich, relevant data for their studies.

It is expected that the structure and information derived from this survey could also contribute to the development and consolidation of solid infrastructures for epidemiological and public health research by building a future national functioning surveillance system that can be reproducible over time. We also expect that this protocol may provide resources for future implementation in other study settings in different countries.

Conclusions

Our findings can help in the design of group-specific national interventions so that people who have seen their psychological health diminished during the pandemic can better cope with this difficult situation, both in Portugal and other parts of the world. Considering that this current health crisis will most likely have long-lasting effects, follow-up studies are needed to obtain a clear picture of the magnitude of the psychological impact of the COVID-19 pandemic.

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Authors' Contributions

All authors contributed extensively to the work presented in this paper. AA designed the protocol and wrote the first draft of the manuscript. MP and RD wrote the protocol, reviewed the manuscript draft, and are the principal investigators of the project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study questionnaire translated in English.
[DOCX File , 743 KB - resprot_v10i10e28071_app1.docx]

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Abbreviations

HADS: Hospital Anxiety and Depression Scale
SARS: severe acute respiratory syndrome

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Protocol

A Sustainable Community-Based Model of Noncommunicable Disease Risk Factor Surveillance (Shraddha-Jagrithi Project): Protocol for a Cohort Study

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Abstract

Background: India has a massive noncommunicable disease (NCD) burden, at an enormous cost to the individual, family, society, and health system at large, despite which prevention and surveillance are relatively neglected. If diagnosed early and treated adequately, risk factors for atherosclerotic cardiovascular disease would help decrease the mortality and morbidity burden. Surveillance for NCDs, creating awareness, positive lifestyle changes, and treatment are the proven measures known to prevent the progression of the disease. India is in a stage of rapid epidemiological transition, with the state of Kerala being at the forefront, pointing us towards likely disease burden and outcomes for the rest of the country in the future. A previous study done by the same investigators in a population of >100,000 revealed poor awareness, treatment of NCDs, and poor adherence to medicines in individuals with CVD.

Objective: This study aimed at assessing a sustainable, community-based surveillance model for NCDs with corporate support fully embedded in the public health system.

Methods: Frontline health workers will check all individuals in the target group (≥age 30 years) with further follow-up and treatment planned in a “spoke and hub” model using the public health system of primary health centers as spokes to the hubs of taluk or district hospitals. All data entry done by frontline health workers will be on a tablet PC, ensuring rapid acquisition and transfer of participant health details to primary health centers for further follow-up and treatment.

Results: The model will be evaluated based on the utilization rate of various services offered at all tier levels. The proportions of the target population screened, eligible individuals who reached the spoke or hub centers for risk stratification and care, and community-level control for hypertension and diabetes in annual surveys will be used as indicator variables. The model ensures diagnosis and follow-up treatment at no cost to the individual entirely through the tiered public health system of the state and country.

Conclusions: Surveillance for NCDs is an essential facet of health care presently lacking in India. Atherosclerotic cardiovascular disease has a long gestation period in progression to the symptomatic phase of the disease, during which timely preventive and

lifestyle measures would help prevent disease progression if implemented. Unfortunately, several asymptomatic individuals have never tested their plasma glucose, serum lipid levels, or blood pressure and are unaware of their disease status. Our model, implemented through the public health system using frontline health workers, would ensure individuals aged≥30 years at risk of disease are identified, and necessary lifestyle modifications and treatments are given. In addition, the surveillance at the community level would help create a general awareness of NCDs and lead to healthier lifestyle habits.

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KEYWORDS

non-communicable diseases; surveillance; accredited social health activist; panchayat (village); primary health centre; spoke and hub; non-communicable diseases; cardiovascular; public health; hypertension; health services; health center; diabetes

Introduction

Noncommunicable diseases (NCDs) are the leading cause of mortality and morbidity in India. Overall, NCDs account for 53% of deaths in India, predominantly due to cardiovascular diseases (CVD) [1,2]. The economic burden associated with CVD in India is enormous, with coronary artery disease, stroke, and diabetes estimated to have caused a cumulative income loss of US $233.6 billion in India between 2005 and 2015 [3]. The disease burden in absolute number is also rapidly increasing, and projections suggest that by the year 2030, there will be 101 and 218 million individuals in India with diabetes and hypertension, respectively [4-6]. The NCD epidemic in India is largely attributed to an aging population, rapid and unplanned urbanization, poor food habits, lack of exercise and sedentary lifestyles, environmental pollution, increased levels of stress, to name a few, along with tobacco and alcohol abuse [7-9].

Due to the rapid demographic and epidemiological transitions, NCDs have become the most important priority in health care planning in India [10,11]. However, the primary and secondary care facilities for early diagnosis, appropriate care, and ethical treatment for NCDs have not grown adequately. In contrast, tertiary services dominated by procedure-driven curative care have grown exponentially, especially in the private sector, considerably increasing out-of-pocket expenditures. This results in late detection, poor secondary prevention, resource-intensive treatment, and often the medical care being unaffordable and inaccessible to large sections of society [12,13].

In a previous epidemiology of noncommunicable diseases in rural areas (ENDIRA) study of >100,000 individuals, poor awareness and control of NCDs were revealed, with 48% of individuals with abnormal plasma glucose values, 37% with high blood pressure, and 85% with high cholesterol values unaware of their disease status. In addition, the majority of newly diagnosed individuals had never checked these parameters prior, partly because of a feeling that all was well with them and also because there was no system in place for surveillance other than for a visit to a health care facility and consultation with a doctor [14-16].

Developing sustainable, context-specific, resource-sensitive, effective, and scalable health system models for disease surveillance, early detection, and secondary prevention strategies are crucial for planning NCD care in India and other low-resource settings. We aim to develop a model surveillance system for NCD risk factors and conditions at the community level and demonstrate the usefulness of a health system model to scale-up diagnosis, treatment, and effective follow-up of chronic NCD conditions in Kerala, India [17,18]. We describe the methodology of our model in detail in this manuscript.

Methods

Study Setting

The study will be conducted in 27 panchayats (lowest units in the three-tier system of local governance in rural India, often consisting of 25,000-40,000 people) and 3 municipalities (larger towns with a population between 100,000 and 1,000,000) of Ernakulam district, Kerala, South India. The study population consists of all permanent residents of the 27 villages and 3 towns above the age of 30 years. The approximate target population size is 600,000. Accredited social health activists (ASHAs) are voluntary health workers at the community level. In Kerala, each of them caters to a population of 1000 individuals [19].

Surveillance System for NCD Risk Factors

We propose a surveillance system, which will involve active screening and diagnosis of NCD risk factors and conditions at the community level. The planned surveillance system is three-tiered: (1) doorstep community screening for blood pressure, weight, and blood glucose through ASHAs using point of care devices, (2) confirmation of test results for eligible individuals provided by ASHAs at the PHC level with borderline values for glucose, blood pressure, and weight or prediagnosed as having 1of the 5 identified major risk factor of atherosclerotic cardiovascular disease (ASCVD), namely diabetes, hypertension, tobacco use, dyslipidemia, or a family history of CVD and (3) a detailed evaluation for CVD, including a lipid profile, thyroid profile, and electrocardiogram, if required, in individuals with 2 or more of the conventional risk factors for ASCVD. At all levels, the ASHA facilitates the care and acts as a care coordinator for the respective individuals in her area. The screening process will be repeated every year, and a minimum of once in 3-month follow-up for all eligible individuals will be coordinated by the ASHAs.

Design

Framework for a New Health System Model

The proposed framework is of a “spoke and hub” model and is planned to be integrated into the existing public health care delivery system. As part of the Shraddha-Jagrithi project, a semi-automated blood analyzer will be provided to each primary health center (PHC; spokes) and a fully automated blood analyzer to the Taluk or district hospitals (hubs). In our model, one district hospital and 2 taluk hospitals will serve as hubs to spokes of 9 PHCs each under them (Figure 1). Trained ASHAs will conduct a detailed survey at the population level and cover all the houses in the selected area. The screening measurements and questionnaire administration for the survey will be done at the doorstep of all residents. The ASHA will administer a structured questionnaire (Multimedia Appendix 1) to capture relevant risk factor data from all study participants. ASHAs will use a tablet computer enabled with a GPS for data collection. Along with data, the device will capture the latitude and longitude of each household surveyed by the respective ASHAs. The ASHA workers will measure the weight and height of all adults aged above 30 years in the household according to standard methods described in the World Health Organization STEPwise approach to surveillance (STEPS) manual [20]. ASHAs will also measure random blood sugar from capillary blood using an ON CALL PLUS glucometer (ACON Labs Inc), and blood pressure will be measured using an OMRON HEM 7124 (OMRON Healthcare), automated digital blood pressure (BP) apparatus. BP readings will be taken twice (5 mins apart), and then an average of the 2 readings will be considered. Written informed consent will be obtained prior to all measurements (Figure 2).

Figure 1. "Spoke and hub" model. ASHA: accredited social health activist; ECG: electrocardiogram; FBS: fasting blood sugar; PHC: primary health center; TSH: thyroid-stimulating hormone.

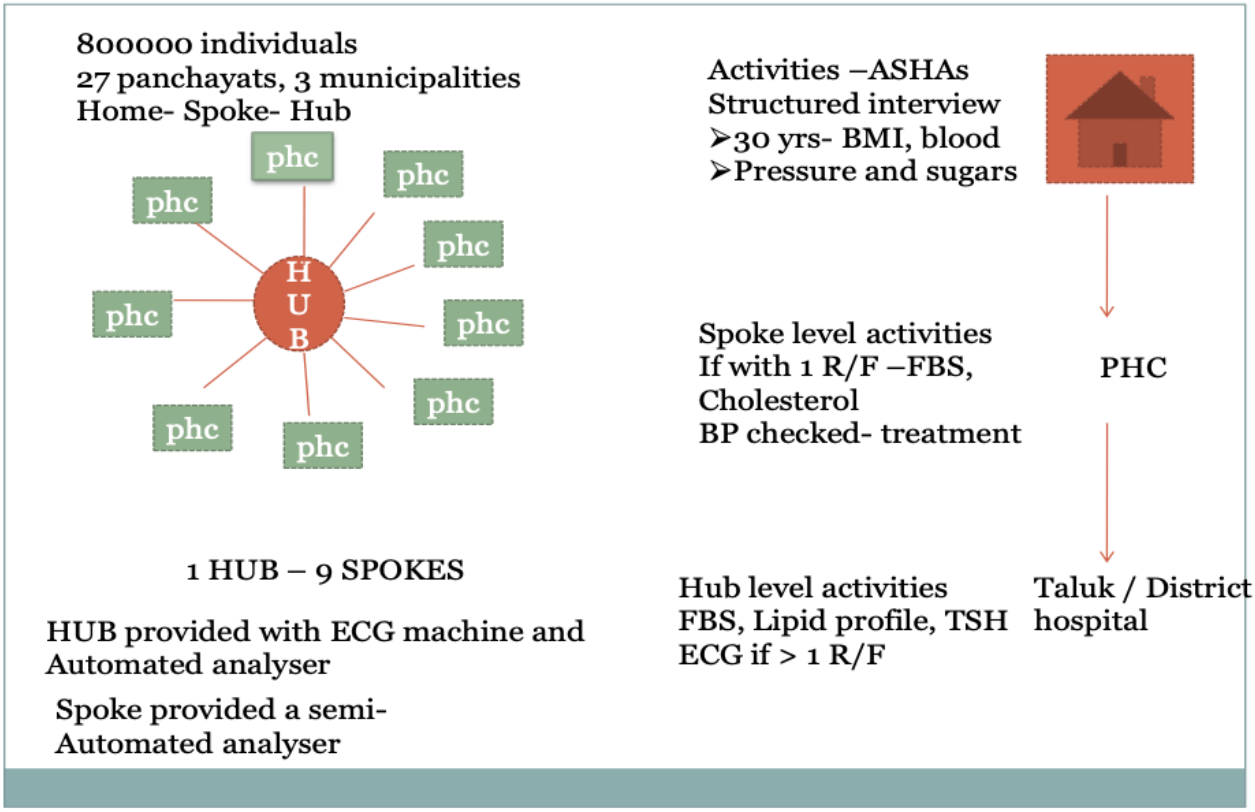

Figure 2. ASHA Kit includes 1 each of item: a tablet PC, glucometer, digital blood pressure apparatus, digital weighing scale, tape, lancets, and strips.

A nodal officer and 2 study coordinators will coordinate the study. The study coordinators will also check data entry and veracity by contacting every 25th household. In addition, the study coordinators will calibrate the tools and troubleshoot the gadgets provided, namely glucometer and sphygmomanometer, at regular intervals. Individuals with surveillance parameters suggestive of a risk of diabetes, hypertension, obesity, current tobacco use, or with a family history of NCDs or ASCVD will be directed for more detailed risk stratification. We will use the following parameters in the estimation of risk for CVD: capillary fasting blood sugar values of >110 mg/dl, 2-hour postprandial value of >160mg/dl, or any random sugar value of >200mg/dl, a systolic blood pressure >140 mmHg, or a diastolic blood pressure >90 mmHg in isolation, or combination, a BMI >25 kg/m2, a family history of CVD in any first degree relatives of the individual (coronary, cerebrovascular, or peripheral artery disease) and tobacco use in any form over the past 30 days.

In case of a single risk factor, the detailed risk assessment will be done at the PHC (spoke hospital) located in the village of residence. Individuals with 2 or more of the risk factors for ASCVD will be directed to the hub center for further assessment, risk stratification, and treatment. In addition to the risk assessment, the NCD clinics of "hub" centers are entrusted with lifestyle interventions, including modules on tobacco and alcohol cessation, advice on dietary modification, and physical activity. Furthermore, medicines required to control NCD conditions as per the prevailing treatment guidelines will be provided at no cost to the patient by the NCD clinics in the PHCs.

The "hub and spoke" model will ensure the inclusion of diagnosis, evaluation, and treatment in the public health care system. The project provides the necessary equipment and instruments for analysis at the community, PHC, and taluk/district hospital tiers. The model will also ensure specialist care of disease conditions for eligible individuals at the hub centers. The PHCs are manned mainly by MBBS doctors, with very few having specialists, while the hub hospitals have specialist posts, with each of them having doctors trained in internal medicine and other specialties, including pediatrics and gynecology. The district National Health Mission and the ENDIRA investigators will provide the necessary training to ASHAs on surveillance methodology and entry and additional support to ASHAs and PHC physicians, with both patient advice and treatment and the modules on lifestyle interventions (eg, diet, exercise, tobacco cessation, etc).

Capacity Building as Part of the Shraddha-Jagrithi Project

As a part of the Shraddha-Jagrithi project, ASHAs will be given training on measuring the height and weight in individuals, blood sugar using a glucometer, blood pressure using the digital blood pressure apparatus, and entering gathered data on tablet computers with a GPS tracking facility. Separate training sessions will be conducted for each panchayat/municipality. In

total, 30 full-day training sessions will be planned for training ASHAs at their respective PHCs/panchayats. The research team, including the investigators, nodal officer, and the project coordinators, will provide the necessary training. After explaining the project, ASHAs will be shown audio-visual modules on recording blood pressure, blood glucose, height, and weight. The audio-visual modules will be made available in the local language (Malayalam). Further, the ASHAs will be grouped into pairs and individually made to check blood glucose, blood pressure, and the height or weight of the partner ASHAs and vice versa.

The ASHAs will distribute pamphlets highlighting common NCDs and their preventive measures and enumerating dietary advice, exercise, cessation of tobacco, and alcohol, in the local language during the screening and measurement visits. In addition, the ASHAs will be primed regarding the primary prevention strategies and counseled on the possible questions that could be asked during those sessions. If ASHAs cannot address participants' questions, they will be asked to connect directly with any study team member through the study coordinators.

Results

Evaluation of the Hub and Spoke Model

The model will be evaluated based on the utilization rate of various services offered at all tier levels. Indicator variables include the proportion of the target population screened, eligible individuals who reached the spoke centers for risk stratification, eligible individuals who received care at the hub, individuals with hypertension and diabetes who received care at the hub and spoke centers under either facility-level control or community-level control for hypertension and diabetes in annual surveys.

Ethical Overview

The Institutional Ethics committee of Amrita Institute of Medical Sciences approved the Shraddha-Jagrithi project (IEC-AIMS-2017-CARD-459). Confidentiality of the data will be ensured as per the existing norms, and it will not be used for any kind of marketing or promotional programs. The data will be stored on a central server in the District hospital, Aluva. The study is registered under the Clinical Trial Registry India (registration number CTRI/2018/07/014856). Signed informed consent is taken from each participant by way of an electronic signature on the tablet PC in the local language.

Statistical Analysis

Baseline characteristics will be explained separately for different strata (ie, by gender, socioeconomic status, and age groups). The differences across strata will be investigated using appropriate statistical tests. A two-sided P value <.05 will be considered statistically significant. The serial trend in the utilization rate of services offered and blood pressure and blood glucose control rates per the indicator variables will be checked by adopting multilevel modeling. We will describe the average pattern of change, difference in direction and rate of change, impact of covariates on differences in change pattern, and influence of circumstances over time on outcome variables. All analyses will be performed using SPSS statistical (version 18.0; IBM).

Discussion

Principal Findings

Our health system model for surveillance and management of NCDs at the community level will help reduce CVD incidence in the future. In addition, the model will help to achieve better control rates of blood pressure and blood glucose in individuals with hypertension and diabetes at the community level. Further, we expect that the framework proposed will help shift the population-level distribution of mean blood pressure and blood glucose towards the left of the distribution curve. This will have important implications in preventing future cardiovascular events.

Our framework will help us obtain reliable surveillance data on CVD risk factors at the population level regularly. It will also facilitate evaluating the impact of ongoing policy changes on screening, prevention, and control of CVD risk factors at the population level. A sound surveillance system is a prerequisite for effective control of chronic diseases and can significantly contribute to the planning and implementation of preventive measures. Although the public health system is grappling with resource constraints, there is room for more efforts to undertake systematic population-based chronic disease surveillance in India [21]. Reliable data on the prevalence of NCD risk factors is important to estimate the future burden of these risk factors or conditions. They are also important to identify and target subpopulations for effective preventive interventions [17,21]. We are trying to leverage the corporate-social responsibility (CSR) schemes for the public good of preventing and controlling CVD at the population level. Further, comprehensive NCD detection programs have been supported by corporates, with civil society leaders providing leadership [22]. We will also engage multiple stakeholders and involve political leaders and local public sector corporates in our CVD prevention and control efforts at the population level.

Expected Outcomes

Our framework will be a significant first step in strengthening the public health system services in preventing and controlling CVDs at the population level. Our unique model of tapping CSR funds to prevent and control CVDs at the population level will be a benchmark for initiating such models in other settings across India. Our framework will also provide an opportunity to evaluate the impact of major policies on the prevention and control of CVDs at the population level.

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Authors' Contributions

JCM, MN, PKS, KVB, PSR, and AB were involved in conceptualizing, planning, and writing the grant proposal. JP, AS, JCM, PSR, and AB are responsible for structuring the methods of the trial. JCM, MN, TR, PKS, AS, and KVB are responsible for the implementation, including training sessions. All the listed authors have contributed to the article being submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Structured questionnaire.
[PDF File (Adobe PDF File), 459 KB - resprot_v10i10e27299_app1.pdf]

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Abbreviations

ASCVD: atherosclerotic cardiovascular disease
ASHA: accredited social health activist
BP: blood pressure
CSR: corporate social responsibility
CVD: cardiovascular disease
ENDIRA: epidemiology of noncommunicable diseases in rural areas
NCD: noncommunicable disease
PHC: primary health center

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Protocol

Design and Rationale of the National Tunisian Registry of Heart Failure (NATURE-HF): Protocol for a Multicenter Registry Study

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Abstract

Background: The frequency of heart failure (HF) in Tunisia is on the rise and has now become a public health concern. This is mainly due to an aging Tunisian population (Tunisia has one of the oldest populations in Africa as well as the highest life expectancy in the continent) and an increase in coronary artery disease and hypertension. However, no extensive data are available on demographic characteristics, prognosis, and quality of care of patients with HF in Tunisia (nor in North Africa).

Objective: The aim of this study was to analyze, follow, and evaluate patients with HF in a large nation-wide multicenter trial.

Methods: A total of 1700 patients with HF diagnosed by the investigator will be included in the National Tunisian Registry of Heart Failure study (NATURE-HF). Patients must visit the cardiology clinic 1, 3, and 12 months after study inclusion. This follow-up is provided by the investigator. All data are collected via the DACIMA Clinical Suite web interface.

Results: At the end of the study, we will note the occurrence of cardiovascular death (sudden death, coronary artery disease, refractory HF, stroke), death from any cause (cardiovascular and noncardiovascular), and the occurrence of a rehospitalization episode for an HF relapse during the follow-up period. Based on these data, we will evaluate the demographic characteristics of the study patients, the characteristics of pathological antecedents, and symptomatic and clinical features of HF. In addition, we will report the paraclinical examination findings such as the laboratory standard parameters and brain natriuretic peptides, electrocardiogram or 24-hour Holter monitoring, echocardiography, and coronarography. We will also provide a description of the therapeutic environment and therapeutic changes that occur during the 1-year follow-up of patients, adverse events following medical treatment and intervention during the 3- and 12-month follow-up, the evaluation of left ventricular ejection fraction during the 3- and 12-month follow-up, the overall rate of rehospitalization over the 1-year follow-up for an HF relapse, and the rate of rehospitalization during the first 3 months after inclusion into the study.

Conclusions: The NATURE-HF study will fill a significant gap in the dynamic landscape of HF care and research. It will provide unique and necessary data on the management and outcomes of patients with HF. This study will yield the largest contemporary longitudinal cohort of patients with HF in Tunisia.

Trial Registration: ClinicalTrials.gov NCT03262675; https://clinicaltrials.gov/ct2/show/NCT03262675

International Registered Report Identifier (IRRID): DERR1-10.2196/12262

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KEYWORDS

heart failure; acute heart failure; chronic heart failure; diagnosis; prognosis; treatment

Introduction

Background

Heart failure (HF) has experienced epidemic growth and has become frequent worldwide. The prevalence of HF among the adult population in developed countries is 1%-2%; however, this rate rises to 10% or more among people aged over 70 [1]. According to recently published data, nearly 26 million people worldwide are living with HF; in particular, in Europe, this number is estimated to be 15 million [1,2]. The global health care cost related to HF is around US $108 billion/year [3]. Despite the development of therapeutic approaches, HF continues to account for a high mortality in up to 50% of patients within 5 years after diagnosis [4]; in particular, one-quarter of patients die within 1 year of diagnosis [5]. Sudden death is the most common cardiovascular cause of death (45%) [6,7].

The frequency of HF in Tunisia is on the rise and has now become a public health concern. This is mainly attributed to an aging Tunisian population (Tunisia has one of the oldest populations in Africa as well as the highest life expectancy in the continent) and an increase in coronary heart disease and hypertension. However, no extensive data are available on demographic characteristics, prognosis, and quality of care of patients with HF in Tunisia (nor in North Africa). Furthermore, the data pertaining to European and American populations cannot be extrapolated to the Tunisian population because of differences in demographics, diagnostic algorithm employed, and therapeutic strategies applied for patients with HF. Therefore, a multicenter observational study focusing on the demographic, prognostic, and therapeutic features of HF in Tunisia is essential. Data from such a study will help us to assimilate our practices, and then to harmonize them in order to optimize the management of patients and to assess the morbidity and mortality of HF as well as the degree of adherence of practitioners to international recommendations in the treatment of this pathology.

Registry Objectives

The National Tunisian Registry of Heart Failure (NATURE-HF) describes the epidemiological profile of acute and chronic HF cases in Tunisia to evaluate their mobi-mortality over 1 year of follow-up. The morbidity of HF is defined as rehospitalization within 1 year of cardiac failure or flare-up occurring after inclusion of the patient, whereas mortality is defined as occurrence of cardiovascular death (sudden death, sudden cardiac arrest, refractory HF, stroke) or death from any cause (cardiovascular and noncardiovascular).

Several secondary endpoints are defined, including evaluation of (1) cardiovascular death over 1 year of follow-up, (2) all causes of death on a 1-year follow-up, (3) re-admission rate for cardiac insufficiency, (4) adherence of physicians to the European recommendations on medical and interventional therapies, (5) impact of HF on patient's health, and (6) determination of the predictors of cardiovascular mortality.

Methods

Study Design and Patient Enrollment

This is a national, observational, longitudinal, multicenter registry study with a follow-up period of 13 months (1 month of inclusion and 12 months of clinical follow-up and exploratory analysis).

We included 1700 patients with HF, outpatients with chronic HF, and those hospitalized for acute HF. The diagnosis of HF is at the discretion of investigators. All included patients should provide written informed consent.

The exclusion criteria were as follows: estimated life expectancy less than 12 months for extracardiac pathology, isolated right HF, pregnancy, end-stage or severe renal insufficiency with creatinine clearance less than 15 mL/minute, undergoing hemodialysis, cardiac surgery scheduled within 3 months, and congenital heart disease.

Any violation of the protocol (eg, included but actually not eligible as per the selection criteria) will be informed to the Steering Committee which will decide on whether or not to exclude the patient concerned.

Sample Size and Data Collection

Patients eligible according to aforementioned inclusion criteria will be selected at the cardiology consultation level or during cardiology or emergency hospitalization. As much as 250 cardiologists (from both public and liberal sectors) will participate in patient selection. Patient inclusion will occur consecutively until the end of the inclusion period. Suitable patients will be selected and requested to sign an informed consent form, confirming their agreement to participate in the study. A detailed questionnaire will then be administered to eligible patients and clinical, biological, and exploratory data will be collected.

The inclusion began on October 2, 2017 (duration 1 month). A regular follow-up was done, wherein patients must visit the cardiology clinic 1, 3, and 12 months after inclusion into the study. This follow-up is provided by the investigator.

Given the observational nature of the NATURE-HF study, no specific treatment or intervention is planned for the management of HF. Patients should be cared for according to the usual medical procedures.

All data are collected via the DACIMA Clinical Suite web interface [8]. The platform complies with international standards FDA 21 CFR part 11 (Food and Drug Administration 21 Code of Federal Regulations part 11), HIPPA (Health Insurance Portability and Accountability Act), ICH (International Conference on Harmonisation), MedDRA (Medical Dictionary for Regulatory Activities), Health Canada, and Tunisian regulations.

Statistical Analysis

The DACIMA Clinical Suite platform enables the collection of online data and their extraction in SAS or SPSS format. Statistical analysis will be performed with SAS software (University Edition; SAS Institute). The statistical analysis is exploratory, involving the calculation of 95% CI.

The data will be described for the whole analyzed population. Continuous quantitative variables (eg, age, weight, left ventricular ejection fraction, biological parameters) will be described by the number of patients documented, mean, median, SD, and extreme values. Categorical variables will be described by the number and percentage of each category.

The normality of the continuous quantitative variables will be verified with the Shapiro–Wilk test. If the hypothesis of normality is rejected, then a simple transformation will be made on the variable to normalize it. If this transformation succeeds in normalizing the variable, then the analysis will be performed on the transformed variable. Otherwise nonparametric tests will be used or possibly an analysis on the quartiles or quintiles will be performed.

Statistical tests will be bilateral with a statistically significant threshold of 5%. An analysis of variance will be performed for the quantitative variables (parametric test for the variables that follow a normal distribution, and nonparametric test in other cases) and a chi-square test will be realized for the categorical variables. The Yates correction or Fisher exact test will be used if the validity conditions for the chi-square test are not met (theoretical number <5).

The sample size (both power and sample) is estimated by the SPSS 2008 software (IBM). To estimate the number of patients to be included in this study, a range of 95% CI (5% significance threshold) is set as the primary endpoint. The impact of this criterion is estimated at 35%, based on the US registry OPTIMIZE-HF [9], which found a hospital mortality ranging from 2.2% to 4.1%, a global mortality ranging between 6.5% and 9.1%, and an overall incidence of all events evaluated (rehospitalization or death) ranging from 35.3% to 36.6%.

Considering these data, the number of patients to be included in the study would be 1436. However, by predicting a 5% missing data rate and a 10% loss to follow-up, the sample size to be selected will be 1700 patients.

The intermediate analyses will be carried out after formulating the statistical analysis plan.

Data Review

The Data Review Committee includes the Coordinators of the Steering Committee of the study as well as the scientific team of DACIMA Consulting. The purpose of the Data Review Committee is to respond to specific queries in data management, and to validate the statistical procedures developed in the final statistical analysis plan. The Data Review Committee will also be responsible for validating subsequent publications.

Expected Implications

The NATURE-HF is the first large-scale investigation to clarify the contemporary demographic data, management, and outcomes of patients with HF.

Oversight and Leadership

The protocol of the NATURE-HF registry has been approved by the Tunisian Society of Cardiology and Cardiovascular Surgery. The NATURE-HF study has been registered in ClinicalTrials.gov (trial registration number NCT03262675).

Study Sponsorship

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

Results

A total of 95 cardiologists included 1700 patients in the registry with a 1-year follow-up period. All patients provided written informed consent. Patients were officially enrolled in NATURE-HF only if they were aged 20 years or older.

The NATURE-HF registry does not impose any specific intervention. Treatment of patients follows the usual recommendations for the management of HF. Clinical events occurring during the follow-up will be collected in order to evaluate the judgment criteria planned in the protocol. However, at the end of the study, a detailed report of the clinical events will be prepared by the STCCCV (Société Tunisienne De Cardiologie Et De Chirurgie Cardiovasculaire [Tunisian Society of Cardiology and Cardiovascular Surgery]) and the document provided to the National Center for Pharmaco-Vigilance.

Discussion

HF is a major health concern worldwide and one of the most important causes of hospitalization [10]. Acute HF is responsible for over 1 million hospitalizations each year in the United States, with a similar number also being reported in Europe [11]. These hospitalizations are responsible for an increased economic burden and are associated with high mortality rates, up to 20% in the 6 months following hospital discharge [12]. HF management is challenging given the heterogeneity of the patient population, absence of an universally accepted definition, incomplete understanding of its pathophysiology, and lack of evidence-based guidelines. Most patients appear to respond well to initial therapies consisting of loop diuretics and vasoactive agents [13,14]. However, these treatments fail to decrease postdischarge mortality and re-admission rates. In the last few years, many drugs have been evaluated to treat HF; unfortunately, results were disappointing in terms of efficacy and safety [15-22].

This large, contemporary longitudinal study of Tunisian patients with HF will provide a unique opportunity to answer many clinical questions. The NATURE-HF study is important in several respects. First, systematic observational and outcomes data can be generated from this registry study, which is especially valuable given that previous data for Tunisian patients with HF are limited. Second, treatment of HF changes dramatically, and thus HF management needs to be evaluated in real-world studies. Third, the NATURE-HF study provides a good opportunity to compare treatment and response variation among HF populations in Africa for comparison with different countries and evaluate adherence to recent guidelines.

The NATURE-HF study will fill a significant gap in the dynamic landscape of HF care and research. It will provide unique and necessary data on the management and outcomes of patients with HF. This study will yield the largest contemporary longitudinal cohort of patients with HF in Tunisia.

Conflicts of Interest

None declared.

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Abbreviations

FDA: Food and Drug Administration
HF: heart failure
HIPPA: Health Insurance Portability and Accountability Act
ICH: International Conference on Harmonisation
MedDRA: Medical Dictionary for Regulatory Activities
STCCCV: Société Tunisienne De Cardiologie Et De Chirurgie Cardiovasculaire (Tunisian Society of Cardiology and Cardiovascular Surgery)

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Protocol

Effects of Telerehabilitation on Patient Adherence to a Rehabilitation Plan: Protocol for a Mixed Methods Trial

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Abstract

Background: Strong evidence supports beginning stroke rehabilitation as soon as the patient's medical status has stabilized and continuing following discharge from acute care. However, adherence to rehabilitation treatments over the rehabilitation phase has been shown to be suboptimal.

Objective: The aim of this study is to assess the impact of a telerehabilitation platform on stroke patients' adherence to a rehabilitation plan and on their level of reintegration into normal social activities, in comparison with usual care. The primary outcome is patient adherence to stroke rehabilitation (up to 12 weeks), which is hypothesized to influence reintegration into normal living. Secondary outcomes for patients include functional recovery and independence, depression, adverse events related to telerehabilitation, use of services (up to 6 months), perception of interprofessional shared decision making, and quality of services received. Interprofessional collaboration as well as quality of interprofessional shared decision making will be measured with clinicians.

Methods: In this interrupted time series with a convergent qualitative component, rehabilitation teams will be trained to develop rehabilitation treatment plans that engage the patient and family, while taking advantage of a telerehabilitation platform to deliver the treatment. The intervention will be comprised of 220 patients who will take part in stroke telerehabilitation with an interdisciplinary group of clinicians (telerehabilitation group) versus face-to-face standard of care (control group: n=110 patients).

Results: Our Research Ethics Board approved the study in June 2020. Data collection for the control group is underway, with another year planned before we begin the intervention phase.

Conclusions: This study will contribute to the minimization of both knowledge and practice gaps, while producing robust, in-depth data on the factors related to the effectiveness of telerehabilitation in a stroke rehabilitation continuum. Findings will

inform best practice guidelines regarding telecare services and the provision of telerehabilitation, including recommendations for effective interdisciplinary collaboration regarding stroke rehabilitation.

Trial Registration: ClinicalTrials.gov NCT04440215; https://clinicaltrials.gov/ct2/show/NCT04440215

International Registered Report Identifier (IRRID): DERR1-10.2196/32134

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KEYWORDS

adherence; interprofessional shared decision making; rehabilitation; stroke; telerehabilitation

Introduction

Stroke impacts nearly 400,000 Canadians annually [1]. It is the leading cause of adulthood disability and is associated with substantial morbidity and mortality [2]. Three-quarters of stroke survivors will live with minor to severe impairments or disabilities, requiring rehabilitation services [3]. Strong evidence supports beginning rehabilitation as soon as the patient's status has stabilized and continuing following discharge from acute care [4]. Returning home shortly after a stroke event places the patient in the most favorable environment to foster the success of the rehabilitation therapy [5] and should be favored over inpatient rehabilitation [6]. For this reason, enabling access and optimizing adherence to rehabilitation services is crucial to ensure positive patient and family outcomes [4]. That said, the need to travel long distances regularly to attend rehabilitation sessions with various professionals [7], the lack of coordination and communication among these outpatient services [4], and the failure to engage the patient and family members in a structured decision-making process [8] limit uptake and delivery of optimal services.

Telerehabilitation, which refers to the use of technology to provide long-distance rehabilitative services [9], is recommended by the Canadian Stroke Guidelines as a means to ensure equal and timely access to optimal stroke services [6]. In this research project, we focus on teletreatment, the provision of remote interprofessional rehabilitation and communication services using videoconferencing technologies.

Despite emerging evidence on the clinical and economic benefits of telerehabilitation [10,11], knowledge gaps remain, especially in a population of community-dwelling stroke patients [12]. Promising results following telerehabilitation include improved function [13-15] and recovery from motor deficits, social function [16,17], quality of life [18], and depression scores [16]. These studies, however, are often characterized by very small sample sizes (ie, fewer than 50 patients investigated), suboptimal treatment length (eg, 1-month duration, whereas guidelines recommend 8-12 weeks), or various definitions of what telerehabilitation entails [10,15,19-27]. As a result, many benefits of the intervention still need to be investigated using robust and large trials [12,14,28-32].

Furthermore, interprofessional shared decision making (SDM) has been shown to help teams to deliver better-quality care and resulted in significant improvements in patients' rehabilitation process [33,34] (eg, patients' knowledge and understanding, participation in the decision-making process, and satisfaction with and trust in the health care team). SDM refers to the process by which health decisions are deliberated upon and made jointly by the patient and one or more health professionals, taking into consideration the best available evidence and the patient's values and preferences [35,36]. Although the effects of SDM have not been extensively documented [33,37] in stroke care, shared decisions are considered the crux of patient-centered care, and SDM has been correlated with greater adherence to treatment plans in other populations [38-43]. Structured interactions among team members through a telerehabilitation platform can create a unique opportunity to improve interprofessional communication and diagnosis skills by supporting the simultaneous participation of all team members, including the patients and family [43,44].

We propose a mixed methods clinical trial to assess the effectiveness of a telerehabilitation platform to increase adherence to rehabilitation stroke care as well as to increase patient participation in interprofessional SDM. The specific objectives of this project are to (1) evaluate the clinical, process, and cost outcomes of an interprofessional technology-enabled stroke rehabilitation intervention in comparison with usual care and (2) identify and describe key contextual factors related to the outcomes of this intervention.

Methods

Study Design

An interrupted time series design with a convergent qualitative component is proposed to test the effectiveness of the intervention. The intervention consists of observing the same dependent variable over time, with a break in the series of observations corresponding to the introduction of an intervention. If the intervention is effective, a change in the series' pre- and postintervention averages can be observed [45]. Moreover, such design will accommodate pre-existing trends and control for possible variations within and among sites (eg, rehabilitation treatment efficacy, low adherence to treatment plan, and team composition). This study was registered at ClinicalTrials.gov (NCT04440215).

Setting

Five selected sites in Quebec, Canada, will start with a control period (preintervention: usual care) until they independently reach their target sample size; this is expected to take between 12 and 18 months. Participants recruited during this period will belong to the control group. The sites will then enter the intervention period until recruitment completion, which is expected to occur after a further 12 to 18 months. Participants recruited during this second period will belong to the

intervention group. Site monitoring will carefully document practices during both trial phases.

Participants

The study population consists of male and female adults, 18 years and older, who (1) have had a stroke event, (2) are considered to be safe for home discharge by the acute or inpatient care team, (3) have a relative or caregiver who is present in the home should physical rehabilitation treatments be required, and (4) can speak French or English. Patients with severe cognitive decline prior to the stroke event will be excluded. Patients with communication difficulties resulting from the stroke event (eg, aphasia) will not be excluded. When possible, a patient's relative or informal caregiver will also be recruited to document their experience of care. Inclusion and exclusion criteria will be similar to above with the exception of the stroke event [46].

Patients will be recruited at each rehabilitation center. At admission, the rehabilitation care coordinator will identify eligible patients and will present the study to the patients and their families. The consent form will be signed prior to the first intervention session. A research assistant will contact the patient and family by telephone to confirm consent and for data collection.

Intervention

Control Phase

Rehabilitation teams will be instructed to provide care as they have been doing previously (ie, usual care). This translates into (1) no telerehabilitation, (2) interdisciplinary meetings not systematically organized and/or not involving a complete team of professionals, and (3) care plans not necessarily elaborated using interprofessional SDM principles.

Intervention Phase

The telerehabilitation platform will be installed at each site in rooms devoted to telerehabilitation activities and equipped with rehabilitation gears. The software OpenTera is a cloud-based multipoint, multi-view, and multi-stream (ie, video and audio) telecommunication system with proven usability and robustness for telerehabilitation applications [7]. The platform is not linked to a specific commercial platform or to special network configurations. It supports multisite interventions (ie, more than one patient at a time), making group sessions and interprofessional meetings feasible. A second camera will be installed on both clinician and patient kits for patients needing speech therapy. The rehabilitation team members will be trained to adapt rehabilitation exercises. Preintervention and ongoing training and coaching will be provided by a trainer who has extensive experience of training rehabilitation teams for various health care conditions; this will be done using the platform.

All rehabilitation teams will receive training in an interprofessional approach to SDM, which recognizes that multiple professionals may be involved in care planning and can support patients and their families in making decisions that are right for them. The teams will receive training to promote knowledge and skills on these topics, and sessions will be modeled after the interprofessional training program used successfully in two recent trials of SDM among home care teams [47,48]. The 3-hour program has two components: (1) a general online tutorial on SDM, based on the Ottawa Decision Support Tutorial [49], and (2) a skill-building workshop that includes a lecture, a video, and a role-play exercise. The brief lecture will be delivered by two experts in SDM and will provide definitions and a conceptual framework for the interprofessional SDM approach. The video will present a clinical vignette illustrating how the interprofessional SDM approach translates into a clinical scenario involving a patient and multiple professionals working together to collectively support a decision. The role-playing exercise will then allow participants in the training session to work in small groups and put into practice lessons learned using a fictional scenario. For this study, materials for the lecture and role-play exercise will be adapted and tailored to the stroke care context, including best practices in care planning as well as SDM [50].

From the patient's perspective, a mix of home or rehabilitation center visits and telerehabilitation will be planned by the rehabilitation team for a maximum of 16 weeks. The rehabilitation services offered will be based on availability at each site. Evaluation, re-evaluation, and manual therapy treatments will be done face-to-face. To ensure internal validity, telerehabilitation sessions are expected to represent at least 80% of participants' rehabilitation plans.

For each participant enrolled, at least one multidisciplinary meeting will be organized to present the rehabilitation treatment plan. The patient and family will participate in the meeting and the decision-making process using the telerehabilitation platform. The team will generate an interprofessional individualized treatment plan for each enrolled participant. A randomized sample of 60 meetings—30 from the control group and 30 from the intervention group—will be selected for recording. This type of nonparticipant observation will allow for a better understanding of the process of interprofessional SDM over the course of the trial.

Primary Outcome

The choice of the primary outcome, patient adherence to the stroke rehabilitation plan at 12 weeks, was identified through a pilot study previously conducted by our research team as the most meaningful outcome and to better document the reason why telerehabilitation might be effective. Adherence to telerehabilitation has been operationalized in many different ways across studies [6,51]. We will define adherence as time spent (in minutes) doing any stroke rehabilitation exercises (online + offline). This includes, but is not limited to, physical, writing, and speech therapy as well as mental health–related exercises recommended by the rehabilitation professional. Online session time will be recorded through the telerehabilitation platform. Offline time will include face-to-face sessions doing rehabilitation as well as time exercising on one's own as instructed by the rehabilitation professional. Offline sessions completed at home will be captured with the use of a journal and recorded by one of the rehabilitation professionals each week. This monitoring step has been used as a method of quality assurance by other scholars in stroke research [52]. Patients' adherence to a rehabilitation program will also be

measured by the Stroke Rehabilitation Exercise Adherence Measure (StREAM) questionnaire at weeks 4, 6 (to allow for test-retest reliability assessment), and 12 [53]. Moreover, health care professional perception of the participants' adherence to the rehabilitation program will be evaluated on a numerical 10-point rating scale each week during the intervention period.

Secondary Outcomes

Secondary clinical outcomes, the instruments used to measure them, and times of measurement are listed in Table 1 [46,54-63].

Focus groups will be conducted with 6 to 12 purposefully selected rehabilitation team members from each site at the end of the intervention phase. Stroke rehabilitation team members will be selected to capture a variety of professions and roles within the team and to ensure information-rich discussions. Themes such as the attributes of telerehabilitation, facilitating contextual conditions, opinion leadership, and platform adaptation for both clinical and collaborative work will be explored with patients and families as well as professionals. Quarterly in-depth interviews with the five site clinical champions will document their ongoing experience.

Similarly, qualitative interviews with 5 to 8 purposefully selected intervention patients and their families, when available, per site will further document the patients' and families' experiences of the technology, interprofessional SDM, and relationship with their outcomes.

Table 1. Secondary outcomes.

Outcome	Instrument	Time of measurement
Patients		
Reintegration into normal life	Reintegration to Normal Living Index [54]	Baseline and 12 weeks
Ability to perform daily activities	Functional Independence Measure [46]	Baseline and 12 weeks
Participation in shared decision making (SDM)	Questionnaire by Strull et al [55]	Following the establishment of the patient treatment plan
Decisional conflict	SURE (Sure of myself; Understand information; Risk-benefit ratio; Encouragement) questionnaire [56]	Following the establishment of the patient treatment plan
Satisfaction with treatment plan	Satisfaction with Decision scale [57]	Following the establishment of the patient treatment plan
Depression	The Beck Depression Inventory [58]	Baseline, 12 weeks, and 24 weeks
Satisfaction with health care received	Health Care Satisfaction Questionnaire [59]	12 weeks
Health care use		
	Institut national de santé publique du Québec population questionnaire (section A) [60]	12 and 24 weeks
	Provincial health administrative data	12 and 24 weeks
Adverse events	Patient's calendar (collected weekly by a rehabilitation professional): incidence of falls, dizziness, pain (visual analog scale), and fatigue (Borg Rating of Perceived Exertion Scale, 1-10)	Weekly basis up to 12 weeks
Individual costs	Questionnaire developed by the authors for this study	24 weeks
Patient's relatives		
Quality of services received	Quality of Services Questionnaire for Relatives poststroke [61]	12 weeks
Rehabilitation professionals		
Statistics related to the use of the telerehabilitation platform (who, when, and duration)	Questionnaire developed by the authors for this study	Weekly basis
Interprofessional collaboration	Assessment of Interprofessional Team Collaboration Scale, short version [62]	Every 3 months for the full duration of the study
Perception of interprofessional care SDM	Collaboration and Satisfaction About Care Decisions questionnaire [63]	Following the establishment of the patient treatment plan

Sample Size Estimates

We calculated the sample size for a univariate comparison of the primary outcome between the two study groups at 12 weeks. The required sample size was calculated using G*Power (version 3.1.9.4; Heinrich-Heine-Universität Düsseldorf) based on a conservative estimated effect size of the intervention (Cohen *d*) of 0.4. This sample size was calculated assuming the following: (1) a two-sided type I error probability of 5% and a power of 80%, (2) a duration of 12 weeks, (3) a 2:1 ratio of intervention to control group participants, (4) two study groups, (5) a <5% loss to follow-up, and (6) intracluster correlations of

0.10. Therefore, 330 participants will be recruited: 110 and 220 participants in the control and intervention groups, respectively.

Analyses

Baseline site and participant characteristics will be summarized descriptively. Patient outcomes will be summarized by group and site. Statistical analysis of the data will follow intention-to-treat principles. A linear mixed model will be used, with individuals' data nested into a study site, to isolate the effect of the intervention on both clinical and process outcomes from other changes that may take place during the trial. Key contextual factors, such as patient's sex and age, state of employment prior to stroke, stroke severity, concomitant rehabilitation treatments received outside the rehabilitation center, and time since stroke event (in days), will be considered in regression models as potential confounders. Interaction terms will be included in the model for any statistically significant contextual factors. Presence of dichotomous stroke outcomes (eg, dizziness) will be compared between study groups using a chi-square test. Multiple imputation will be considered if missing data represent more than 10% of a given variable. Sensitivity analysis will be conducted to assess the impact of missing data on estimates of intervention effects with a multiple imputation statistical technique and without imputation (ie, available case analyses), as well as for outlying observations.

Interviews and treatment plan meetings will be fully transcribed. A descriptive analytical approach will be used to develop a framework of organizational factors leading to a successful telerehabilitation intervention, both at the patient and professional levels. Audio recordings and transcripts will be reviewed simultaneously to assess validity of the transcription process and will be analyzed using an iterative approach [64]. Data saturation will be determined as defined by Constantinou et al [65]. This will be followed by an intersite analysis to identify what is common between the sites examined and what is specific to certain sites, and to compare the different configurations between sites. Finally, matrices with contextual factors will be generated to identify particular patterns [66].

Ethics

The Research Ethics Board of the Hôpital Charles-Le Moyne of the CISSS (Centre intégré de santé et des services sociaux) de la Montérégie-Centre has approved this research project and is providing oversight on the ethical concerns of this project, including for any potential revisions of the protocol. Patients and caregivers have both been thoroughly informed of all aspects of the research protocol in which they might be included and have been assigned a patient number for anonymization purposes. All data will be collected by phone or using paper questionnaires. Data will be kept in a password-protected database in the research team's private servers, and paper questionnaires will be kept in a locked container in the offices of the research team.

Results

As of July 2021, a total of 37 patients have been enrolled, from which 12 patients have completed the study. Data collection for the control group is expected to last for another 6 to 12 months; this will be completed before we begin the intervention group data collection, which should last 2 to 3 years. We do not intend to begin analysis before the end of the data collection period.

Discussion

Impact

From a clinical perspective, the use of a telerehabilitation platform will improve adherence to stroke rehabilitation programs by (1) better anchoring patients and families in their own environments (eg, by using day-to-day objects to perform rehabilitation exercises) to favor functional rehabilitation; (2) facilitating an intensive rehabilitation program by decreasing the time and hurdles of traveling; (3) providing an optimal care plan that matches the patient and family condition, context, and expectations; and (4) favoring more active participation by the patient and family as well as by all members of the rehabilitation team.

Limitations

Precautions will be taken to train each stroke team immediately prior to the intervention launch, to minimize contamination between the control and the intervention phases, which is one of the main risks of this study. The use of a linear mixed model should prevent an overestimation of the effect of the intervention [67], a common limitation of study designs that take place over a long period of time.

Another potential weakness is that organizational change entails an inner shift in the organization's stakeholder values and aspirations as well as a series of behavior changes in response to external shifts in processes, strategies, and environments [68]. The proposed intervention will require adjustments from the rehabilitation professionals in order to gradually shift the teams' ways of delivering care. Frequent scheduled interactions between rehabilitation and study teams should create an empowering context for the care providers involved in this trial; minimize anxiety, resistance, and unproductive behaviors; and ensure that the intervention implementation is rooted in the organization's culture.

Findings from this study will inform best practices guidelines by providing empirical data on effective collaboration processes as well as optimized telerehabilitation delivery via telecare services. The production of a guideline called "How to better implement telerehabilitation within a stroke continuum" with dissemination through governmental agencies will aid sites not involved in this trial to implement telerehabilitation, in addition to classical dissemination, such as conferences and journal publications. This will also optimize the impacts of this intervention on stroke rehabilitation continuums beyond the trial sites.

This study represents a unique, highly relevant, and innovative opportunity to minimize both knowledge and practice gaps in rehabilitation stroke care, including interprofessional SDM. This study will produce robust data on the effectiveness of the intervention and in-depth data on the contextual factors and mechanisms that are related to its effectiveness, for whom and how. Participating health care providers will gain the

wherewithal to engage patients and families and to develop their interprofessional decision-making skills, which are crucial to meet patients' needs and significantly improve patient adherence.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Canadian Institutes of Health Research/Instituts de recherche en santé du Canada (CIHR/IRSC).
[PDF File (Adobe PDF File), 738 KB - resprot_v10i10e32134_app1.pdf]

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Abbreviations

CISSS: Centre intégré de santé et des services sociaux
SDM: shared decision making
StREAM: Stroke Rehabilitation Exercise Adherence Measure

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Protocol

Detection of Spatiotemporal Clusters of COVID-19–Associated Symptoms and Prevention Using a Participatory Surveillance App: Protocol for the @choum Study

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Abstract

Background: The early detection of clusters of infectious diseases such as the SARS-CoV-2–related COVID-19 disease can promote timely testing recommendation compliance and help to prevent disease outbreaks. Prior research revealed the potential of COVID-19 participatory syndromic surveillance systems to complement traditional surveillance systems. However, most existing systems did not integrate geographic information at a local scale, which could improve the management of the SARS-CoV-2 pandemic.

Objective: The aim of this study is to detect active and emerging spatiotemporal clusters of COVID-19–associated symptoms, and to examine (a posteriori) the association between the clusters' characteristics and sociodemographic and environmental determinants.

Methods: This report presents the methodology and development of the @choum (English: "achoo") study, evaluating an epidemiological digital surveillance tool to detect and prevent clusters of individuals (target sample size, N=5000), aged 18 years or above, with COVID-19–associated symptoms living and/or working in the canton of Geneva, Switzerland. The tool is a 5-minute survey integrated into a free and secure mobile app (CoronApp-HUG). Participants are enrolled through a comprehensive communication campaign conducted throughout the 12-month data collection phase. Participants register to the tool by providing electronic informed consent and nonsensitive information (gender, age, geographically masked addresses). Symptomatic participants can then report COVID-19–associated symptoms at their onset (eg, symptoms type, test date) by tapping on the @choum button. Those who have not yet been tested are offered the possibility to be informed on their cluster status (information returned by

daily automated clustering analysis). At each participation step, participants are redirected to the official COVID-19 recommendations websites. Geospatial clustering analyses are performed using the modified space-time density-based spatial clustering of applications with noise (MST-DBSCAN) algorithm.

Results: The study began on September 1, 2020, and will be completed on February 28, 2022. Multiple tests performed at various time points throughout the 5-month preparation phase have helped to improve the tool's user experience and the accuracy of the clustering analyses. A 1-month pilot study performed among 38 pharmacists working in 7 Geneva-based pharmacies confirmed the proper functioning of the tool. Since the tool's launch to the entire population of Geneva on February 11, 2021, data are being collected and clusters are being carefully monitored. The primary study outcomes are expected to be published in mid-2022.

Conclusions: The @choum study evaluates an innovative participatory epidemiological digital surveillance tool to detect and prevent clusters of COVID-19–associated symptoms. @choum collects precise geographic information while protecting the user's privacy by using geomasking methods. By providing an evidence base to inform citizens and local authorities on areas potentially facing a high COVID-19 burden, the tool supports the targeted allocation of public health resources and promotes testing.

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KEYWORDS

participatory surveillance; infectious disease; COVID-19; SARS-CoV-2; space-time clustering; digital health; mobile app; mHealth; epidemiology; surveillance; digital surveillance; public health

Introduction

Background

Since 2020, many countries worldwide, including Switzerland, have experienced multiple fluctuations of SARS-CoV-2 transmission associated with cycles of increased followed by relaxed measures [1,2]. These cycles will remain until appropriate immunization levels through natural infection or vaccination are achieved [3]. There is growing concern that adherence to public health recommendations, including SARS-CoV-2 testing, is declining (ie, testing fatigue) [4,5]. Thus, it is essential to define alternative strategies to encourage timely testing, recommendation compliance, and monitor spread of the virus.

Traditional disease surveillance systems, relying on SARS-CoV-2 cases confirmed by real-time polymerase chain reaction (RT-PCR) or antigenic tests, suffer from underreporting and a delay of notification due to the time between the onset of symptoms and case declaration [6]. There is a need for alternative sources of information complementing the traditional COVID-19 surveillance systems [7,8]. The use of collaborative information through participatory surveillance, facilitated by mobile phone apps and web-based tools, offers a quick way to collect data at a population scale and disseminate critical information [9]. Participatory syndromic surveillance systems have shown promising results for several public health events [10,11], and many have already been described since the start of the COVID-19 pandemic [9,12-16]. However, most apps require users to report health information daily or weekly, which could increase dropout rates. Moreover, only a few apps have been configured to collect geographic information at high resolution [12,15,16]. Increased knowledge about the potential risk of infection at a local scale (ie, precise geographic coordinates associated with a specific date) can play an essential role for residents and local authorities [17] who lack information to make appropriate decisions [18]. Several studies have emphasized the importance of rapid prospective spatiotemporal epidemiological surveillance, which can help prioritize locations for targeted interventions, rapid testing, and resource allocation [7,19-22]. Despite this opportunity, individuals may be reluctant to report exact addresses together with symptoms owing to security and privacy concerns [23,24]. Therefore, such participatory surveillance systems must be developed in a way that minimizes the risks and best guarantees the individuals' rights to privacy.

The @choum (English: "achoo") study proposes a digital participatory epidemiological surveillance tool using precise space-time data to monitor COVID-19–associated symptoms at their onset in the canton of Geneva, Switzerland. The @choum tool is a 5-minute survey that profits from being integrated into a free and secure preexisting app for COVID-19 resources and information developed by the University Hospitals of Geneva (HUG). Upon registration to @choum, participants can report COVID-19–associated symptoms at their onset by tapping on the @choum button visible on the home screen. They are then redirected to the official COVID-19 recommendations websites. This study provides an innovative combination of best practices in participatory surveillance and spatiotemporal epidemiology. This report describes the rationale and methodology of the @choum study, and presents the development procedure of the @choum digital tool, which has been publicly available since February 11, 2021.

Objectives

The specific study objectives are as follows: (1) to prospectively detect active and emerging spatiotemporal clusters of reported COVID-19–associated symptoms by running a daily automated spatiotemporal cluster detection algorithm; and (2) to retrospectively analyze the outbreaks detected over the 12-month data collection phase, and examine the association of outbreak characteristics with sociodemographic and environmental factors.

Methods

Study Design

The @choum study evaluates a digital participatory epidemiological surveillance tool to detect and prevent spatiotemporal clusters of individuals, aged 18 years or above, with COVID-19–associated symptoms living and/or working in the canton of Geneva, Switzerland. Its design integrates both prospective and retrospective analytical features. The study began on September 1, 2020, and will be completed on February 28, 2022.

Setting and Governance Team

This study takes place in the canton of Geneva. It is carried out by an interdisciplinary team based at the HUG in close collaboration with experts from the University of Geneva (UNIGE), the Swiss Federal Institute of Technology Lausanne (EPFL), and the University of Paris (UP). The different components of the study have been distributed across the governance team members as follows: digital tool development, Direction of Information Systems, HUG; communication campaign strategy, Communication Directorate, HUG; spatiotemporal analyses, Geographic Information Research and Analysis in Population Health, HUG, UNIGE, and EPFL; and smart testing referral strategy, Division of Primary Care, HUG. Collaborators at the Center for Research and Interdisciplinarity at UP provide expertise on citizen-based participation strategies. Prior research has demonstrated our extended team's productive collaboration, generating impactful research that integrates expertise in the fields of population health, spatial epidemiology, and virology [21,22,25].

Participants and Eligibility

Participant eligibility criteria include (i) aged≥18 years, (ii) living and/or working in the canton of Geneva, (iii) having access to a smartphone with a Swiss or French phone number and a connection to the internet, and (iv) being capable of providing informed consent. Individuals not meeting these criteria are prevented from completing study registration but are redirected to official recommendation websites. All participants provide electronic informed consent (eIC) to participate in the study. Participant enrollment began on February 11, 2021, and will be completed on February 28, 2022, meaning that participants can enroll during the entire data collection phase.

Our approach to eIC follows the guidelines provided by the local institutional ethics committee, and requires participants to (i) read the study electronic information letter and declaration of consent displayed within two scrolling menus, (ii) check the consent box, and (iii) tap the "I accept" button. The study does not ask for the name or signature of participants to ensure individual privacy. Participants are informed that they can opt out at any time via their profile or by contacting the research team. In the absence of an opt-out request, all participants are followed throughout the data collection phase.

Study Preparation

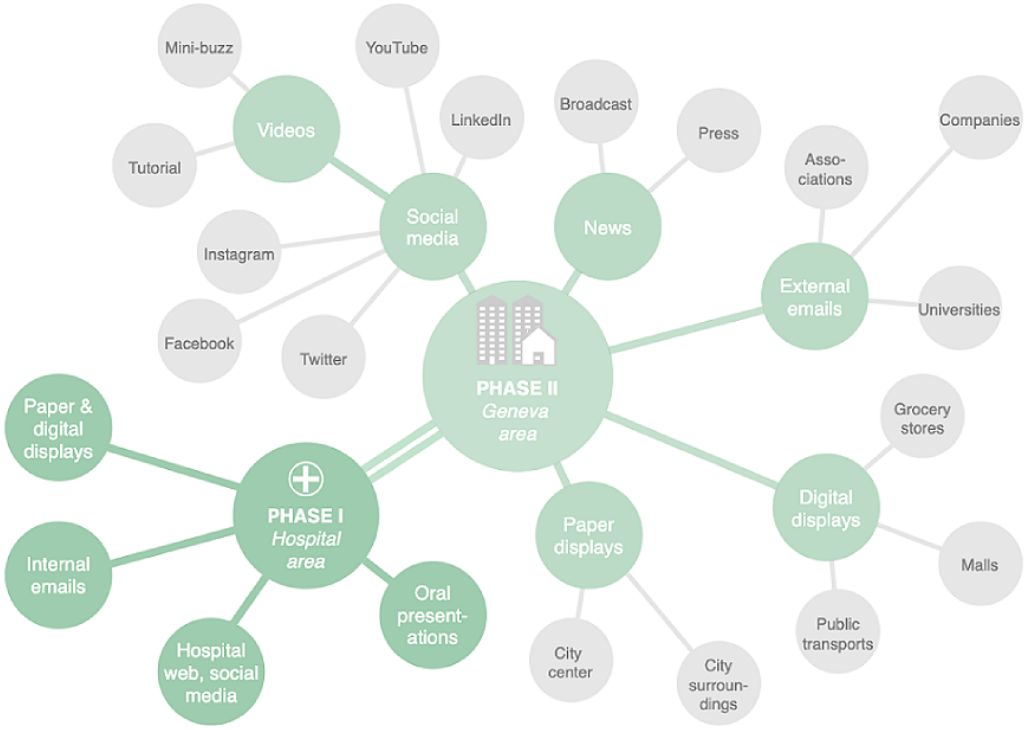
A 5-month preparation phase, starting on September 1, 2020, has preceded the 12-month data collection phase. The development milestones included: (1) frontend development (content, design, and branching logic); (2) backend development (database); (3) spatiotemporal clustering analysis implementation and testing; (4) data exchange between the app, server, and Python script running daily clustering analyses; and (5) complete security assessment. Following an iterative process, the tool's content was reviewed and refined by experts in infectious disease, epidemiological research, citizen science, health communication, and app design. Multiple technical and analytical tests have been performed at various development stages of the tool in preproduction and production modes.

A 1-month pilot phase was performed among 38 pharmacists working in seven pharmacies located in the canton of Geneva before the study launch. The pharmacists were asked to follow expected app utilization scenarios (eg, reporting either a positive or negative test result) and to complete a 10-minute satisfaction online questionnaire.

Recruitment Campaign

We developed a comprehensive two-phase multichannel communication campaign launched together with the @choum tool on February 11, 2021 (Figure 1). This campaign aims to maximize the chances of attaining individuals interested in participating in the study. We conducted a first communication phase of 2 weeks within the hospital (HUG) setting before launching the second phase targeting the entire population of the canton of Geneva. This progressive two-phase communication approach has enabled our research team to maintain control over potential technical challenges associated with an increased participation rate. The first phase of the communication strategy included paper and digital advertisements (flyers, posters, screens), internal emails (intranet), hospital-based web and social media pages (landing page linked to other HUG-based pages, YouTube, LinkedIn, Instagram, Facebook, and Twitter), and oral presentations. The second phase expanded the communication strategy to additionally include outdoor advertisement at locations of high pedestrian traffic in the city center and surroundings areas (main streets, parks, bus and train stations), digital advertisement (public transport, grocery stores, and malls), external emails (intranet of partner associations, local companies, and universities), articles and interviews in traditional media (radio, tv, press), and social media also broadcasting five 2-minute video tutorials and a short and engaging 45-second video [26]. The selection of outdoor advertisement locations was guided by prior research from our group, which identified the canton's areas at risk of increased SARS-CoV-2 transmission [25]. All communication materials were designed and developed by the HUG communications team in collaboration with the other governance team members. The core advertising message expresses the possibility of contributing to a collective action helping researchers in the fight against the pandemic.

Figure 1. The @choum (English: "achoo") comprehensive communication campaign started on February 11, 2021, within the hospital setting (Phase I) before its extension to the entire population of the canton of Geneva on March 1, 2021 (Phase II).



Participation Steps and Elements

Individuals wishing to participate in the study can download the CoronApp-HUG, freely available on Android (Google Play Store) [27] and iOS (Apple Store) [28] devices in Switzerland and France. @choum has been added as a new functionality to the preexisting CoronApp-HUG mobile app, released by the HUG on March 12, 2020, which provides users with valuable resources and the latest information on COVID-19. Upon download completion, users accept the General Terms and Conditions of Use of the app and access the tool via a button visible on the home screen.

Participation in the @choum study is simple, takes approximately 5 minutes, and consists of three steps: (1) consent and registration, (2) report of COVID-19–associated symptoms by tapping on the @choum button, and (3) COVID-19 recommendations. Registration is completed only once, whereas episodes of COVID-19–associated symptoms can be reported at multiple time points throughout the data collection phase. An information button is displayed on the upper right corner of some selected screens, which provides participants with more detailed explanations relevant to each participation step. The main study screens are presented in Figure 2, and the study branching logic and elements are presented in Figure 3.

Figure 2. The main @choum (English: "achoo") study screens, translated into English: (A) CoronApp-HUG home screen with access to the study, (B) the screen preceding study consent and registration, (C) the main screen providing the possibility to report COVID-19–associated symptoms by tapping on the @choum button (green button stating "@choum I have one or more symptoms"), and (D) example screen redirecting to COVID-19 recommendations.

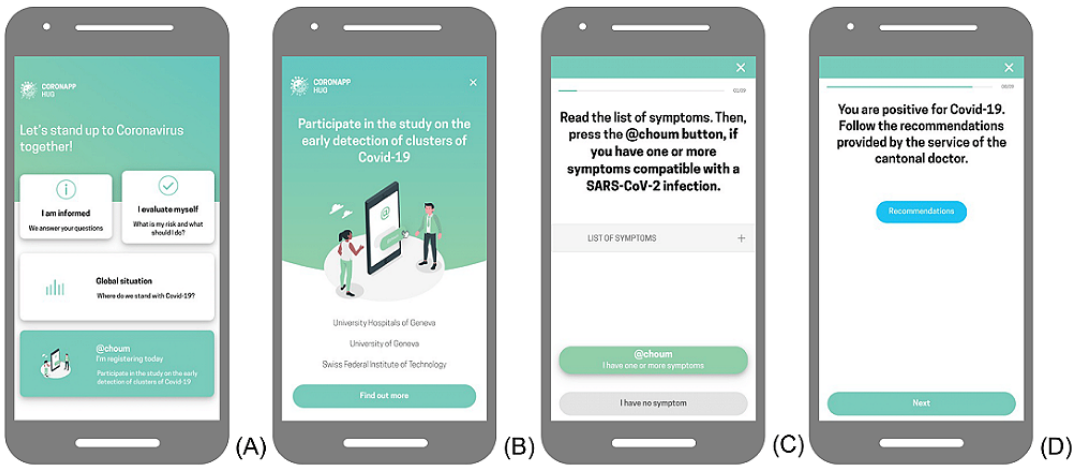
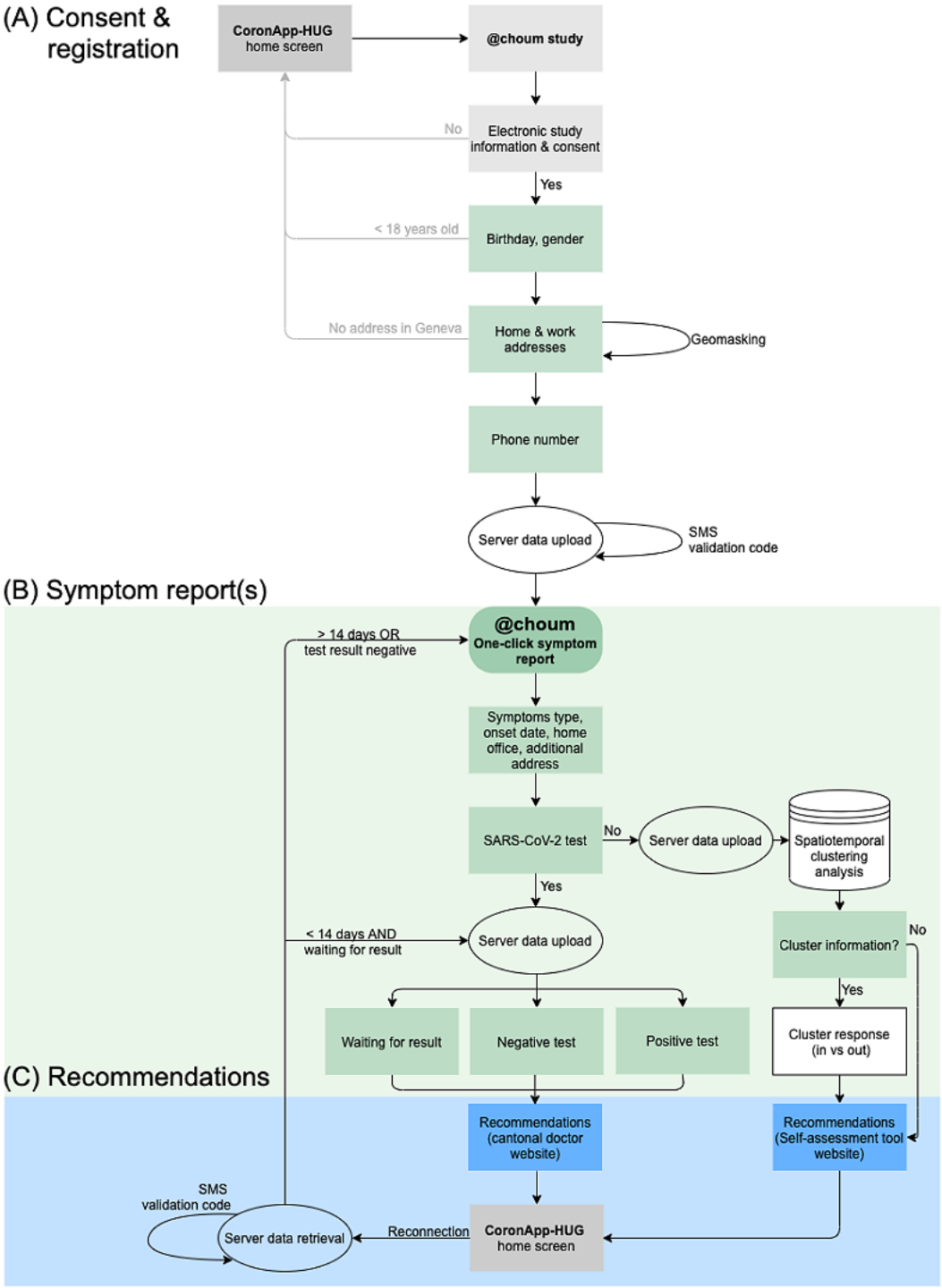


Figure 3. Simplified scheme of the @choum (English: "achoo") study branching logic and elements. Once (A) registration is completed, (B) COVID-19–associated symptoms can be reported at multiple time points throughout the data collection phase (from February 11, 2021, to February 28, 2022), and (C) recommendations are provided based on each report. HUG: Geneva University Hospitals.



First, individuals interested in participating receive information on the study goals, benefits, and impacts of participation. Second, they go through the electronic letter of information and the declaration of consent to give their eIC via the "I accept" button, designed for this purpose. Individuals are informed that they will be asked for their work and home addresses but that these addresses are not used for tracking purposes and are replaced with masked geographic coordinates. The geographic masking procedure consists of displacing geographic coordinates randomly within a circular radius of 200 meters around their original position [29]. Individuals providing eIC can register for the study by reporting their gender, age, residential and/or work addresses, and phone number. Registration is then confirmed by a unique code sent via SMS text message. Upon

completion of study registration, the @choum button for symptoms reporting becomes accessible on the home screen. No action is required from participants, as long as they are not experiencing any COVID-19–associated symptoms. A user profile is created, allowing participants to check and modify their home and work addresses at any given time.

When perceiving COVID-19–associated symptoms, participants can start the symptoms report process by tapping on the @choum button. Users are required to go through a list of symptoms before proceeding further into their symptom report. This step aims to ensure that participants are informed about the symptoms typically associated with COVID-19. Participants are asked a set of questions (detailed in the Data Collection section) concerning their symptoms. If they have not yet been tested for SARS-CoV-2, they are given the possibility to be informed on whether they currently live or work in an area where a high number of other participants have reported COVID-19–associated symptoms (ie, active and emerging spatiotemporal clusters). This feedback is based on the automated spatiotemporal clustering analysis results updated daily and returned to participants via specific screens within the app to encourage user engagement. Symptomatic participants with addresses located within such a cluster are further encouraged to get tested for SARS-CoV-2 and subsequently report the test date and result. This information is used to filter the addresses included in the prospective spatiotemporal cluster detection analyses.

Lastly, participants are redirected to publicly available and official recommendation websites based on their reported information. Participants who have symptoms but have not yet been tested for SARS-CoV-2 are redirected to a survey tool by the Swiss Federal Office of Public Health (SFOPH) [30]. The tool allows individuals to self-assess their risk of SARS-CoV-2 infection and book a test appointment through the HUG website. Participants are presented with a link to the cantonal doctor's websites at each participation step and are invited to follow the official COVID-19 recommendations [31]. Upon symptoms reporting, all participants are thanked for their participation and invited to download the contact-tracing app SwissCovid [32], launched by the SFOPH, which helps interrupt chains of transmission using digital contact tracing of confirmed COVID-19 cases. After a period based on the information provided in the symptom report (Figure 3), the @choum button becomes accessible again and participants have the opportunity to create another report upon experiencing new COVID-19–associated symptoms. All study screens are presented in Multimedia Appendix 1.

Data Collection

Enrollment and follow-up data are collected at study registration and at each report of COVID-19–associated symptoms, respectively (Figure 4). Enrollment data include age (date of birth, age≥18 years), gender (female, male, nonbinary), home and work addresses (street name, street number, postal code vs do not live or work in Geneva), and phone number (Swiss or French prefix number). The data obtained for each symptoms report include perceived symptoms (acute respiratory symptoms [cough, cold, or difficulty breathing], fever, loss of smell or taste, other), date of symptom onset (≤last 14 days), home office (yes vs no), suspected address of infection (street name, street number, postal code vs do not wish to add an additional address), cluster status (I wish vs I do not wish to be notified) if the participant has not yet done the test, SARS-CoV-2 test (yes vs no), date of the test (≤last 14 days and ≥date of symptom onset), and test result (positive, negative, waiting for result). Participants' cluster status (principal addresses [home and/or work] in vs out) is obtained through the spatiotemporal clustering analyses performed every 24 hours. Lastly, data collection ascertains whether the participant has opened the link to the self-assessment tool website (yes vs no) and the cantonal doctor's official recommendations (yes vs no). Participants can change their personal addresses at any time under their @choum profile.

Data on adoption, participation, and usage behaviors are collected from the Google Play Store, Apple Store, and CoronApp-HUG app. Data obtained from these sources include the number of CoronApp-HUG landing page visits per day on each store, the number of CoronApp-HUG downloads per day, and app utilization pattern metrics.

Figure 4. Schedule of study preparation, participant recruitment, and assessments. HUG: Geneva University Hospitals.

	STUDY START-UP					DATA COLLECTION PHASE
Months	$-t_5$	$-t_4$	$-t_3$	$-t_2$	$-t_1$	0-12
PREPARATION						
Study concept and ethic approval	X	X				
Surveillance digital tool development		X	X	X	X	
Pilot testing					X	
Maintenance and surveillance						⟷
RECRUITMENT						
Communication campaign I (hospital area)						⟷
Communication campaign II (Geneva area)						⟷
PARTICIPATION						
Participant Enrolment Assessment[a]						
Age						X
Gender						X
Home and work addresses						X
Phone number						X
Participant Symptom Report Assessment[b]						
Percieved symptoms						
acute respiratory symptoms[c]						X1-i
fever						X1-i
loss of smell or taste						X1-i
other						X1-i
Date of symptoms onset[d]						X1-i
Home office						X1-i
Suspected address of infection (optional)						X1-i
Cluster status (optional)[e]						X1-i
Test SARS-CoV-2, date[f]						X1-i
Test result (positive, negative, waiting for result)						X1-i
Coronarisk website consulted[g]						X1-i
Cantonal doctor recommendations website consulted[g]						X1-i
App User Behavior Assessment						
No of landing page visit/day (Apple and Google stores)						X
No of downloads/day (Apple and Google stores)						X
App navigability patterns						X

[a]Participants must be aged ≥ 18 years, live and/or work in the canton of Geneva, and have a smartphone with a Swiss or French number.

[b]Symptoms can be reported at multiple times throughout the data collection phase.

[c]Described as cough, cold, or difficulty breathing.

[d]The date must be ≤ 14 days.

[e]Participants are given the possibility to be informed on whether they currently live or work in an area where a high number of other participants have reported COVID-19 associated symptoms.

[f]The date must be ≤ the last 14 days and ≥ the date of symptom onset.

[g]Ascertain whether participants have opened the link to the Coronarisk (or self-assessment tool) website survey or to the official COVID-19 recommendations by the cantonal doctor.

Data Monitoring and Handling

Since the tool's launch, data are extracted and analyzed weekly by the research team to monitor adoption, participation, and currently active and emerging spatiotemporal clusters. Information on areas currently facing increased COVID-19–associated symptoms may be shared with local public health authorities to guide local interventions. Individual-level data will not be shared at any time, and an assessment of possible participation biases will be conducted before sharing any information to avoid risks of misguiding public health efforts. The evolution of the participation rates and the geographical distribution of participants are used to adapt the communication campaign activities in intensity and location.

All collected data are treated confidentially and securely stored in the HUG-located server, respecting the general data protection regulation legislations of the European Union (GDPR) and Geneva (LIPAD). A unique validation code sent to the participant is used to confirm the participant device's ownership and reduce abusive system use. The data collected on the frontend of the app are sent to the server at specific time points: upon study registration completion, after being asked about SARS-CoV-2 test results, and every time the validation code is sent (Figure 3). The geocoding (ie, the transformation of addresses into geographic coordinates) is implemented through a completely offline procedure using a reference dataset of Swiss addresses [33]. The geographical masking is conducted before uploading the data to the server, and thus no exact street address or original geographical coordinates are uploaded to the server at any given time. One data manager, responsible for the database maintenance, encrypts the data prior to their extraction

for analyses. An opt-out request by the participant results in complete deletion of the account and data.

Sample Size

The sample size was calculated as ~5000 participants to detect active and emerging spatiotemporal clusters of reported COVID-19–associated symptoms. This analysis assumed a total of 500,000 potential participants aged≥18 years (~400,000 living in and ~100,000 commuting to Geneva for work) [34,35]. Out of this total number, 2% (~10,000) may download the app and half (~5000) are expected to consent to the study. Statistics on health-related mobile app retention rates show that 3% of users are likely to use a health-related app for an entire 30-day use period [36-38]. However, COVID-19 mobile apps have seen better retention rates, with examples such as the UK National Health Service COVID-19 app and the SwissCovid app, which are being used by around 20% of the population [39,40]. A conservative sample size was selected because it is expected to be highly influenced by the evolution of the epidemiological situation.

Data Analysis

Software

Analyses will be conducted using Python 3.8 [41], R 4.0.5 [42], GeoDa 1.18 [43], and QGIS 3.18.1 [44].

Prospective Analyses

The prospective detection of spatiotemporal clusters will be achieved using the modified space-time density-based spatial clustering of applications with noise (MST-DBSCAN) algorithm, designed to detect, characterize, and visualize disease cluster evolution [45]. The MST-DBSCAN algorithm is among various density-based clustering methods to detect disease clusters. This modified version of the spatiotemporal DBSCAN has the advantage of considering the transmission relationship between cases, thus incorporating the effect of the incubation period and the ability to detect irregularly shaped clusters [45]. Additionally, density-based methodologies only require symptomatic reports to function, making them particularly suited to the @choum study that collects reports only from users experiencing symptoms. This method determines clusters using a circular spatial scanning window (*EpsS*) and a time window defined by two parameters, *EpsT1* and *EpsT2*, which determine the threshold value for the longest and shortest transmission period, respectively. Similar to the traditional DBSCAN, the MST-DTSCAN algorithm then classifies points into three categories: core, border, and noise points [45,46]. A *core point* is a point with enough spatiotemporal neighbors to be considered the major structure of a cluster with high incidence. The minimum number of neighbors that a point must have to be classified as a core is defined by the parameter *MinPts*. A *border point* is a point that is part of a cluster without being itself the center of a cluster because it does not have enough neighbors. Finally, *noise points* are outliers located in low-incidence areas [45].

To obtain the most up-to-date information on active and emerging clusters, a Python (v3.8) script, based on the package pySDA 0.1.6 [47], is automatically run every 24 hours using the date and masked geographical coordinates (home, work, suspected location of infection) of the symptom reports. This information is used to notify participants reporting COVID-19–associated symptoms of their cluster status (ie, within a cluster or not). The algorithm's parameters are currently set to *MinPts*=3, *EpsT1*=14, *EpsT2*=1, and *EpsS*=600 meters. The time window is specified according to the current knowledge on incubation and transmission periods [48]. The spatial window of 600 meters represents a good compromise between the resolution of the analysis and privacy preservation [21,25]. The *MinPts* is set to 3 according to the cluster definition used by local health authorities [49]. The parameters used for each daily analysis are stored and adapted according to the latest research on the spatiotemporal scales of COVID-19 transmission. The Python script returns the geographical coordinates of the detected clusters. Only the clusters active at the date of analysis are retained. To avoid geometries in our data, which would require spatial databases, the area of the circular polygon formed by each cluster is approximated using hectometric squares that are uniquely identified and stored using their upper-left coordinates only.

Retrospective Analyses

Descriptive statistics of user participation, retention, and collected participant data will be computed using means (SD) and medians (IQR), and frequencies for continuous and categorical variables. These will enable assessing our sample's representativity compared to the canton of Geneva's general population.

The number of monthly active users and the number of created and deleted accounts will be monitored during the entire study period, which will enable estimating the retention rate of the @choum study. The performance and the conversion rate of the digital communication campaign will be monitored for each employed social media platform (ie, Twitter, YouTube, Facebook, Instagram, and LinkedIn) by collecting metrics on the number of views and the number of users interacting with each communication post. Additionally, the number of downloads of the CoronApp-HUG and the number of @choum registered users will be monitored weekly following these communication campaigns. Together, this will allow us to estimate the conversion rate of the communication efforts.

We will analyze outbreaks across the entire study period using spatiotemporal and purely spatial statistic methods to understand the evolution of the outbreaks detected over the 12-month data collection phase. Unusual utilization patterns such as repeated reports (ie, >2) of symptoms with positive RT-PCR test results will be classified as "spam" and discarded from retrospective analyses. However, this potential risk of high users falsely inflating reports in location and time has been reduced by limiting users to only report COVID-19–associated systems once every 14 days to ensure that reports correspond to a single episode of COVID-19–associated symptoms. Multiple methods will be used to provide a more complete and robust assessment of the underlying spatiotemporal process [50,51], and include the space-time scan statistics [52], local join count statistics [53], and MST-DBSCAN [45]. The latter will provide a fine-scale characterization of the evolution of clusters in

Geneva's canton across the entire study period. This characterization of clusters into classes (eg, emerge, growth, steady, reduce, merge, move, split) will enable the differentiation of populations and areas of high and low temporal concentration of symptoms (ie, epidemic peakedness) [54]. Lastly, we will examine the association between spatiotemporal cluster characteristics and sociodemographic and environmental determinants of COVID-19–associated symptoms (covariates) using procedures presented in detail elsewhere [22,25].

Results

The study began on September 1, 2020, and will be completed on February 28, 2022. The @choum study received final approval on November 12, 2020, by the Cantonal Research Ethics Commission of Geneva, Switzerland (2020-01586). A 5-month preparation phase has preceded the 12-month data collection phase starting on September 1, 2020, and February 11, 2021, respectively. Multiple tests performed at various time points throughout the first 4 months of the preparation phase have helped to improve the tool's user experience. Subsequently, the 1-month pilot phase conducted among 38 pharmacists confirmed that the spatiotemporal clustering analyses worked appropriately, and the feedback helped to improve the user experience and address technical bugs. Since the tool's launch to the entire population of Geneva on February 11, 2021, and as of May 15, 2021, we have enrolled over 1000 eligible participants. The primary study outcomes are expected to be published in mid-2022.

Discussion

The @choum study seeks to develop, implement, and test an innovative participatory epidemiological surveillance tool to rapidly detect and prevent clusters of COVID-19–associated symptoms by using precise geographic information. Multiple tests and a 1-month pilot study conducted among 38 pharmacists working in 7 Geneva-based pharmacies have confirmed the proper functioning of the tool. Since the tool's launch to the entire population of Geneva on February 11, 2021, daily prospective clustering analyses at a local scale help detect active and emerging spatiotemporal clusters, and thus inform citizens and local authorities on areas potentially facing a COVID-19 burden.

The retrospective analyses performed at the end of the study will deliver critical insights into the mechanisms underlying the diffusion dynamics of SARS-CoV-2.

The rationale underlying the @choum study builds on the well-recognized need to rapidly inform key stakeholders (ie, clinical decision-makers, local authorities, and citizens) about geographical areas facing a higher burden of disease [6,9,54]. Prioritizing areas and populations of high COVID-19 burden has been critical since the start of the SARS-CoV-2 pandemic and will continue during the following months as the vaccination campaign expands. For example, the province of Ontario, Canada, has recently expanded vaccination eligibility criteria to all adults living in hotspot neighborhoods [55]. Similarly, our group has shown that clusters observed among a sample of over 3000 confirmed COVID-19 cases were more persistent in the socioeconomically disadvantaged Geneva-area neighborhoods, which could be targeted in priority for intervention [25]. However, most existing participatory syndromic surveillance initiatives are not designed to collect high-resolution spatiotemporal data [56]. The @choum study tackles this challenge by using modern spatiotemporal methods and precise location data while protecting the user's privacy, enabling potentially more efficient and effective management of the SARS-CoV-2 pandemic. A few notable studies have already taken a similar approach using fine-scale geographic information in combination with spatiotemporal clustering analyses [7,16]. For example, Leal-Neto et al [7] used a combination of data from traditional and participatory surveillance to detect spatial clusters; however, the temporal component was not considered due to the potential latency of 14 days on COVID-19 cases. The MST-DBSCAN algorithm employed in the @choum study tackles this challenge by incorporating the incubation period effect.

Since the start of the pandemic, a growing body of literature has highlighted the existence of health inequalities in COVID-19 infection and mortality [57-59]. However, most studies have been performed in the United States and United Kingdom. In Switzerland, a study published by our group in early 2021 revealed important sociodemographic determinants of epidemic spread at the local level [25]. Findings from the @choum study will provide critical insights into the mechanisms underlying the diffusion dynamics of SARS-CoV-2 by performing retrospective analyses of collected data, and exploring the associations between cluster characteristics and sociodemographic and environmental determinants. Indeed, the shape of COVID-19 epidemics is an area of great scientific interest [60,61], and the use of spatiotemporal clustering may offer an innovative tool to better understand the determinants of peaked or prolonged epidemics at a fine geographic scale.

A distinctive feature of the @choum tool lies in the unique possibility for participants who have not yet been tested to be informed on their current cluster status (ie, whether they currently live or work in an area where a high number of other participants have reported COVID-19–associated symptoms). In the context of testing fatigue [5], this returned information on the participants' cluster status could promote testing among symptomatic participants and reduce the delay of notification inherent to traditional epidemiological surveillance systems [8,9]. Moreover, because @choum is integrated into an app for COVID-19 resources and information, and is linked to other official COVID-19 recommendation websites, it supports the centralization of local COVID-19 communications [6]. These may be crucial, as getting mixed messages from various sources can reduce compliance with preventive measures [62,63].

Several limitations of this study merit comment. First, generalization will be limited to the adult population living or working in the canton of Geneva. Second, adoption and utilization of the @choum tool might suffer from a participation bias, as attitudes toward digital COVID-19 public health tools such as contact tracing apps vary among sociodemographic groups [64,65]. However, we developed and implemented several strategies to foster participation across sociodemographic

groups and ensure user retention. We implemented a comprehensive communication campaign using numerous online and offline channels. In implementing this campaign, potential competition between the @choum study and the preexisting contact tracing app (SwissCovid) [32] has been considered; @choum was explicitly designed to avoid this possibility, notably by encouraging the adoption of SwissCovid and explaining their complementarity. We also aimed to allow users to rapidly and easily report symptoms, which could improve participation and retention rates compared to other participatory syndromic surveillance systems requiring frequent use or periodical inputs. Third, geographic data are limited to fixed coordinates, and thus occupations involving high mobility (eg, in-home nurses, taxi drivers) are not represented.

To the best of our knowledge, @choum is the first participatory epidemiological surveillance system combining fine-scale spatiotemporal data with prospective clustering analyses. Such a tool could be helpful to effectively prevent the spread of COVID-19 and related diseases. This tool has the potential to provide timely and precise geographical information to encourage infection control interventions at a local scale and public health recommendations compliance. The study findings will also advance other research contributions investigating the complex relationship of environment and health using novel digital technologies. It is thus hoped that the @choum study will be a valuable support in the fight against COVID-19.

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Authors' Contributions

Study concept and design: DDR, AJL, FE, JLS, MS, BGT, SS, LK, J-FP, SJ, IG; tool development: DDR, AJL, FE, JLS, MP, AR, GV, IG; communication campaign: GV, AJL, IG; statistical analyses: DDR; interpretation of data: DDR, AJL, FE, JLS, IG; drafting of the manuscript: DDR, AJL, FE, JLS, IG; critical manuscript revision: DDR, AJL, FE, JLS, MS, BGT, SS, LK, J-FP, SJ, IG; study administration: AJL, IG; study supervision: IG. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
All screens related to study participation.
[PDF File (Adobe PDF File), 5730 KB - resprot_v10i10e30444_app1.pdf]

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Abbreviations

eIC: electronic informed consent
EPFL: Swiss Federal Institute of Technology Lausanne
HUG: Geneva University Hospitals
MST-DBSCAN: modified space-time density-based spatial clustering of applications with noise
RT-PCR: real-time polymerase chain reaction
SFOPH: Swiss Federal Office of Public Health
UNIGE: University of Geneva
UP: University of Paris

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Corrigenda and Addenda

Correction: Person-Generated Health Data in Women's Health: Protocol for a Scoping Review

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Related Article:

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In "Person-Generated Health Data in Women's Health: Protocol for a Scoping Review" (JMIR Res Protoc 2021;10(5):e26110), one error was noted.

The phone number for the Corresponding Author in the originally published manuscript has been removed and replaced by the phone number "1 604 875 4111."

The correction will appear in the online version of the paper on the JMIR Publications website on October 18, 2021, 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

Pediatric Chronic Critical Illness: Protocol for a Scoping Review

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Abstract

Background: Improvements in the delivery of intensive care have increased survival among even the most critically ill children, thereby leading to a growing number of children with chronic complex medical conditions in the pediatric intensive care unit (PICU). Some of these children are at a significant risk of recurrent and prolonged critical illness, with higher morbidity and mortality, making them a unique population described as having chronic critical illness (CCI). To date, pediatric CCI has been understudied and lacks an accepted consensus case definition.

Objective: This study aims to describe the protocol and methodology used to perform a scoping review that will describe how pediatric CCI has been defined in the literature, including the concept of prolonged PICU admission and the methodologies used to develop any existing definitions. It also aims to describe patient characteristics and outcomes evaluated in the included studies.

Methods: We will search four electronic databases for studies that evaluated children admitted to any PICU identified with CCI. We will also search for studies describing prolonged PICU admission, as this concept is related to pediatric CCI. Furthermore, we will develop a hybrid crowdsourcing and machine learning (ML) methodology to complete citation screening. Screening and data abstraction will be performed by 2 reviewers independently and in duplicate. Data abstraction will include the details of population definitions, demographic and clinical characteristics of children with CCI, and evaluated outcomes.

Results: The database search, crowd reviewer recruitment, and ML algorithm development began in March 2021. Citation screening and data abstraction were completed in April 2021. Final data verification is ongoing, with analysis and results anticipated to be completed by fall 2021.

Conclusions: This scoping review will describe the existing or suggested definitions of pediatric CCI and important demographic and clinical characteristics of patients to whom these definitions have been applied. This review's results will help inform the development of a consensus case definition for pediatric CCI and set a priority agenda for future research. We will use and demonstrate the validity of crowdsourcing and ML methodologies for improving the efficiency of large scoping reviews.

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KEYWORDS

pediatrics; critical care; intensive care units; chronic critical illness; research design

Introduction

Background

Over the past two decades, the increased survival of even the most critically ill children is greatly attributed to the improvements in the delivery of intensive care [1]. An unintended consequence of this success has been a shift in the population of patients admitted to the pediatric intensive care unit (PICU), with an increasing number of children with chronic or complex medical conditions and significant long-term morbidities following critical illness [1-4]. There is a growing recognition that a subset of pediatric critical illness survivors experience persistent multiorgan system dysfunction and functional morbidities following critical illness that subsequently render them with either a prolonged need for critical care support as inpatients or dependence on medical technology to be cared for as outpatients [5-8]. These children are increasingly recognized as a uniquely high-risk PICU population, also referred to as children with chronic critical illness (CCI) [4,6].

Despite being a uniquely high-risk population in the PICU, research on pediatric CCI remains limited. This patient population has been understudied, largely because of the lack of an accepted consensus case definition. The limited research to date, using variable definitions, suggests that the prevalence of children with CCI is increasing [1,2] and that these children have relatively higher morbidity and mortality rates after critical illness [6,7,9]. These convergent and complex issues exert significant strain on the health care system, health care providers, and caregivers [10-12]. To position the field of pediatric CCI research for systematically evaluating this important patient population, a consistent approach is needed with respect to the population that is being described and studied. Only then is it possible to determine modifiable risk factors for poor patient outcomes, and develop and evaluate interventions to improve the care and survivorship of this important PICU patient population.

Objectives

Given that we expect a heterogeneous and complex body of work, we have used a scoping review methodology to explore and describe the nature of pediatric CCI research [13,14]. Our primary aim is to evaluate how pediatric CCI is defined in the literature, including concepts such as prolonged or long-stay PICU admission, as it has been proposed that prolonged PICU admissions are important qualifiers for pediatric CCI [4,6]. The secondary aims of this scoping review are to describe the methodologies used to develop and validate any existing definitions of pediatric CCI. We will also seek to describe the prevalence of CCI in the PICU based on existing definitions and describe the key demographic and clinical characteristics of the patient populations studied. Finally, we describe the nature of the reported outcomes in children with CCI.

Methods

Protocol

This is an original scoping review following the standard methodology proposed by Arksey and O'Malley [15] and elaborated upon others [13,16]. This protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews [17]. We uploaded the protocol as a preprint to the Open Science Framework on February 1, 2021 [18]. We plan to document protocol amendments in the Open Science Framework with the date, description, and rationale. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Eligibility Criteria

Types of Participants or Population

We will include studies that evaluated critically ill children (ie, <18 years old) admitted to any PICU, explicitly identified with *CCI*. We will also include studies that evaluated prolonged, protracted, chronic, or long-stay PICU admission, as this concept has been identified as an important qualifier for pediatric CCI. However, we excluded records if they (1) evaluated adult or neonatal intensive care unit populations only, or included children among these populations but did not report separate data for children; (2) evaluated pediatric patients in intermediate care, step-down, high-dependency, or chronic ventilator or respiratory units; and (3) did not include or reference a definition of pediatric CCI or prolonged PICU admission, as applicable to the study (eg, as a case definition in a prevalence study).

Types of Interventions, Comparators, and Outcomes

We will not apply any restrictions regarding interventions, comparators, or outcomes.

Types of Publications

We will include observational and experimental studies, qualitative studies, and protocols that provide a working definition of pediatric CCI or prolonged PICU admission. Then, we will exclude literature reviews, unpublished literature, editorials, commentaries and opinion pieces, conference proceedings, abstracts, and books. Given the emerging nature and recognition of CCI in children, we will exclude records published before 1990. We will exclude studies that were not published in English or French.

Search Strategy

We developed a preliminary search strategy in two electronic databases (MEDLINE and CINAHL) and piloted this in consultation with a health research librarian (RC). We developed the final search strategy in MEDLINE, which was peer-reviewed by 2 additional health research librarians not involved in the study, and then translated it into the other databases, as appropriate (Textbox 1). We will search four databases that index citation titles or abstracts using English Medical Subject

Headings terms and keywords from their dates of inception to March 2021: Ovid MEDLINE, Embase, CINAHL, and Web of Science. We will review the reference lists of all included studies to identify any studies that may have avoided the final database search.

Textbox 1. Search strategy (MEDLINE). adj: adjacent; epub: electronic publication; exp: explode; .mp: multi-purpose; PICU: pediatric intensive care unit.

Database

- Ovid MEDLINE epub ahead of print, in-process and other nonindexed citations, Ovid MEDLINE(R) daily and Ovid MEDLINE(R) 1946-present

Search strategy

- intensive care units/and (child* or pediatric or paediatric).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- Intensive care units, pediatric/
- PICU.mp.
- ((p?ediatric* or child or children*) adj3 (acute* or critical* or intens*)).mp.
- or/1-4
- exp Critical Care/
- Critical Illness/
- (critical* or intens*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- or/6-8
- exp chronic disease/
- length of stay

  /
- ((long or duration or length) adj3 (stay or hospitali*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- or/10-12
- 5 and 9 and 13
- ((chronic* or persist* or long term or longterm or long-stay or prolong* or protract* or extend* or extensive or lengthy or difficult*) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 5 and 15
- 14 or 16
- ((p?ediatric* or child or children*) adj5 (chronic* or persist* or long term or longterm or prolong* or protract* or extend* or extensive or lengthy or difficult* or ((long or duration) adj3 stay)) adj5 (acute* or critical* or intens* or ill or illness* or sick or sickness* or care)).mp.
- 17 or 18

Study Selection

Search Strategy and Study Selection Criteria Piloting

The team used an iterative approach to evaluate and refine the preliminary search strategy and study selection criteria. Using the results of the preliminary search strategy, 4 members of the core study team independently reviewed an initial set of 100 randomly selected citations using the initial study selection criteria. Each record was reviewed in triplicate. We screened the 100 citations in two steps (title and abstract, then full text), discussed discrepancies, and refined the eligibility criteria. The lead investigator (DZ) reviewed the reference lists of studies meeting all inclusion criteria, identified any relevant studies, and, together with the health sciences librarian, refined the search strategy if these relevant studies were missed by the database search. Following this initial round, we reevaluated the revised study selection criteria using a second set of 100 random citations assessed independently and in triplicate. The conflict rates were 45.5% (5/11 full texts) and 7.7% (1/13 full texts) in full-text assessment during the two iterative piloting rounds. Following these two iterative piloting rounds, the team established a consensus on the study selection criteria. A total of 8 eligible studies were identified during the piloting.

Crowdsourcing

Given the large number of citations identified in the final search strategy, we will use a hybrid approach comprising crowdsourcing and a machine learning (ML) algorithm to expedite the screening of records. The crowdsourcing methodology for systematic reviews has been previously validated [19,20] and used in a variety of health research reviews to accelerate the citation screening and provide more timely research output, while still allowing for rigorous review conduct [21-23]. We will recruit a curated crowd of approximately 30 English- and French-speaking reviewers with content and methodological expertise from international PICU networks (eg, Canadian Critical Care Trials Group, Pediatric Acute Lung Injury, and Sepsis Investigators group), email, social media (using the hashtags #PedsICU, #PICSp, and #CCI), and a dedicated study crowdsourcing event page on insightScope [24]. Authorship incentives will be offered to crowd reviewers who achieved specific screening milestones (ie, group authorship if ≥500 abstracts and ≥50 full texts screened, named authorship if ≥1000 abstracts, ≥100 full texts screened, and participated in data abstraction).

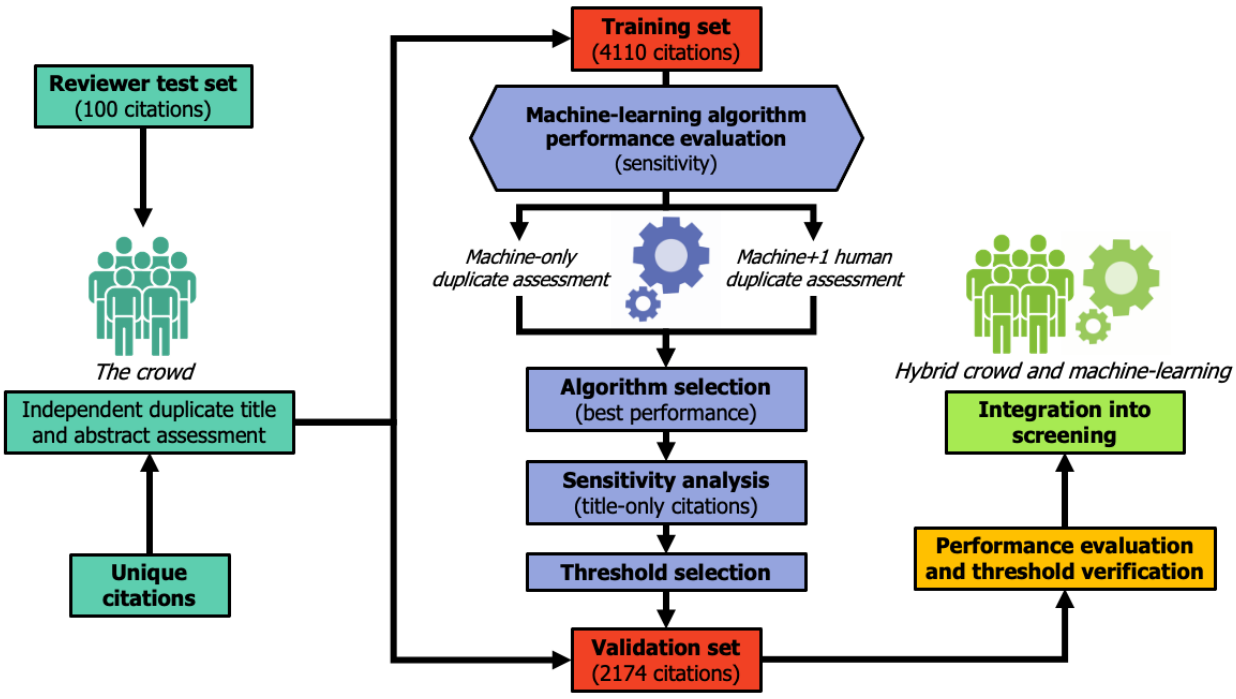
Before formal screening, prospective reviewers will be provided with a copy of the protocol and selection criteria. Prospective reviewers will first perform screening on a test set designed using the piloted study selection criteria [25]. The test set will contain 100 citations from the pilot phase with 10 eligible (true positive) citations. Prospective reviewers must achieve a sensitivity of ≥80% before they are given access to the full set of study records. Reviewers who do not achieve ≥80% sensitivity will be provided with additional training before being given access to the full set of study records.

We will use a dedicated channel on Slack (Slack Technologies), a cloud-based team communication platform, to streamline the study progress updates and reviewer communication [26,27].

ML Algorithm

ML algorithms are being increasingly used to assist in citation screening for systematic reviews, particularly in large reviews [28-31]. We will develop an ML algorithm to semiautomate citation screening for this scoping review at the title and abstract stage only, which is consistent with previously described approaches (Figure 1) [31]. The independent and duplicate screening of at least 4000 citations through to the full text by crowd members will constitute a *training set* that we will use to evaluate five ML algorithms (bag of words, term frequency-inverse document frequency, word to vector, document to vector, and fast text). These algorithms assess the citation title and abstract (where available) and rank each citation by relevance based on the text captured in the study selection criteria and project goal, with the highest ranking citations being retained based on a threshold set by the investigator (eg, a threshold of 70% would retain the 30% highest ranking citations). The titles and abstracts of citations from the four electronic databases were downloaded in English; therefore, no language adaptations were required to apply the ML algorithms to non–English-language studies.

Figure 1. Integration of crowdsourcing and machine learning in the scoping review.



We will select the two highest performing algorithms from the training set and evaluate their sensitivity and specificity at a variety of thresholds, when used alone and in combination with a single human reviewer. We will also separately evaluate the performance of the two highest performing ML algorithms for citations without an abstract (ie, title only) to evaluate whether a unique threshold would be required. For both ML algorithms, we will determine the threshold at which the sensitivity is >95% when used in combination with a single human reviewer. This

approach is consistent with the individual sensitivity of *expert* reviewers, as described in previous studies [20,23,32,33].

Once developed, we will evaluate the performance of the two candidate ML algorithms on an additional *validation set* constituting at least 2000 citations screened independently in duplicate by crowd members. Our a priori methodology will be to proceed with the duplicate independent human assessment of citations above the selected threshold score, and machine plus one independent human assessment for citations below the threshold score. We will also plan to apply an additional lower threshold score if the sensitivity data for the candidate ML algorithms consistently exceed our sensitivity goal (ie, 95%). This lower threshold will serve to exclude the most irrelevant citations through assessment by the ML algorithm alone.

Integration of Hybrid Crowdsourcing and ML Algorithm Citation Screening

The integration of crowdsourcing and ML algorithm methods into citation screening in this scoping review is outlined in Figure 1. We will download records from the electronic search into Endnote for duplicate removal and export the citation list for screening to insightScope [34], a platform for executing large reviews through crowdsourcing. We will upload citation abstracts and full-text articles with inclusion and exclusion criteria for insightScope. Screening will be performed in two steps (title and abstract, then full text) against the inclusion criteria by 2 independent reviewers. We will record reasons for the exclusion of citations excluded from full-text screening. As previously described, no language adaptations to the screening process for non-English studies will be required for the title and abstract stage, as citations retrieved from electronic databases are in English. However, full texts in French will be reviewed independently and in duplicate by French-speaking crowd reviewers. All screening conflicts (either between 2 humans or a machine and 1 human) will be resolved by third-party adjudication by the members of the core study team, as required.

Data Charting

We will perform data abstraction using the piloted electronic data abstraction forms created in insightScope. The data abstraction forms were created by one investigator (DZ) and piloted by the members of the core investigative team (JDM, BR, NP, KO, and KC) against a total of 8 eligible studies. We have described the data items in Textbox 2. Before formal data abstraction, we will provide all data abstractors with training (ie, a data abstraction manual and training video). Data will be abstracted by 2 independent reviewers from the crowd, both independently and in duplicate. We will abstract data from the full-text publication and any related publications, referenced published protocols, or supplementary materials. Where necessary, one reviewer will extract graphical data using SourceForge Plot Digitizer, which will be checked by the second reviewer for accuracy. Moreover, where necessary, data will be abstracted from publications in French by French-speaking crowd reviewers independently and in duplicate. The study lead (DZ) resolved conflicts in data abstraction, as required. In the event of missing or unclear data related to our outcomes of interest, we will make a maximum of three attempts to contact the study authors for clarification.

Textbox 2. Data items.

Study characteristics

- Author name and contact information
- Title
- Country of origin
- Journal and year of publication
- Study design
- Clinical setting and type of pediatric intensive care unit (eg, medical-surgical, cardiac only, and neuro-pediatric intensive care unit)
- Participant inclusion and exclusion criteria
- Total patients included
- Study period (dates)

Study population definition

- Definition of pediatric chronic critical illness (eg, as defined by study or referenced from another publication)
- Definition of prolonged pediatric intensive care unit or long-stay admission (eg, duration, as defined by study or referenced from another publication)
- If and how the definition was developed or validated by the primary study
- Prevalence of study participants with chronic critical illness or prolonged pediatric intensive care unit admission, as applicable to the study

Study population demographics and characteristics

- Age and sex
- Reason for pediatric intensive care unit admission
- Source of pediatric intensive care unit admission (eg, emergency department, neonatal intensive care unit, floor or step-down unit)
- Functional status characteristics (using validated tools, as categorized by the article)
- Severity of illness characteristics (using validated tools, as categorized by the article)
- Comorbidity and medical complexity status, including if and how patient medical complexity and comorbidity was described in the study
- Prevalence and types of organ support technologies in study participants (eg, mechanical ventilation, feeding support, circulatory support [vasoactive drugs, extracorporeal membrane oxygenation, ventricular assist device], and extrarenal filtration)
- Types of study participants (eg, children with chronic critical illness or prolonged pediatric intensive care unit admission, families, siblings, and health care providers)

Outcomes evaluated

- Stated primary outcome, including how it was measured and result
- Patient outcomes, including mortality (pediatric intensive care unit, hospital, and overall), discharge disposition (eg, high-dependency unit, ward, rehabilitation facility, and home), and health-related quality of life
- Family and sibling outcomes (any, as categorized by the article)
- Health care provider outcomes (any, as categorized by the article)
- Health care system outcomes, including the length of stay (pediatric intensive care unit and hospital), pediatric intensive care unit bed-day use or consumption, pediatric intensive care unit readmission rate or occurrence, and pediatric intensive care unit cost analyses

Results Synthesis

We will report data related to study characteristics descriptively using counts with the percentages or measures of central tendency and variance (eg, means/medians with SDs/IQR), as appropriate. We will use tables to narratively summarize data related to study population definitions, including the prevalence of the population studied (if applicable) and contextual variables related to study type, setting, and evaluated patient population. We will describe the important elements of the methodology used to derive the case definition of CCI and prolonged PICU admission, including but not limited to the size of study, study design, setting(s), and if criteria for agreement or convergence established a priori. We will group included studies into one of the two definition domains based on their explicitly identified study population of interest (ie, CCI or prolonged PICU admission) and summarize data for each, separately. We plan to categorize patient- and family-based outcomes evaluated in the included studies according to the domains of the PICU Core Outcome Set [35] (ie, overall health, cognitive function, physical

function, and emotional function), as applicable, to help formulate a priority agenda for future research.

Statistical analyses will be performed using SPSS Statistics, version 26 (IBM), as necessary. We will not perform any meta-analyses of epidemiological or outcome data collected from primary publications, in keeping with the descriptive nature of this scoping review. In keeping with a scoping review methodology, we will not complete the risk of bias assessment for included studies or undertake the certainty of evidence assessment for this scoping review [13,14]. However, the limitations of the nature and extent of populations and outcomes evaluated in current pediatric CCI research will be addressed in the Discussion section of the paper.

Results

Database search, citation screening, and the data abstraction phases of this scoping review started on March 3, 2021, and were completed on April 16, 2021. Data verification is ongoing, with data analysis as follows: the analysis of the review, with results, is anticipated to be completed by fall 2021.

Discussion

Crowdsourcing and ML Algorithm Methods

A total of 32 crowdsourced reviewers completed the test set of 100 citations, achieving a mean sensitivity of 91.6% (SD 0.09). Two reviewers with exactly 70% sensitivity on the test set were provided additional training on the study protocol and study selection criteria before citation screening. Of these, 28 reviewers, with a test set sensitivity of 92.1% (SD 0.09), participated in the citation screening. Reviewers originated from 11 countries and 5 continents.

As a prerequisite to incorporate an ML algorithm into citation screening, we determined the optimal algorithm and sensitivity threshold for operationalization. The sensitivities of the five evaluated ML algorithms when used alone or in combination with a single human reviewer to assess citations from the training set are presented in Figures 2 and 3, respectively. The 4110-citation training set included 28 citations meeting the inclusion criteria following an assessment by 2 reviewers after full-text review (ie, true positives). The two highest performing ML algorithms were bag of words and term frequency-inverse document frequency, demonstrating 93% and 100% sensitivity, respectively, at a threshold of 80% when citation assessments were performed by the ML algorithm alone. The sensitivities for both these ML algorithms were 100% at a threshold of 80% when citation assessments were performed by the ML algorithm in combination with a single human reviewer.

Figure 2. Machine learning algorithm training set performance (machine-only citation assessment). The bag-of-words and term frequency-inverse document frequency demonstrate the highest sensitivities up to a threshold of 80%.

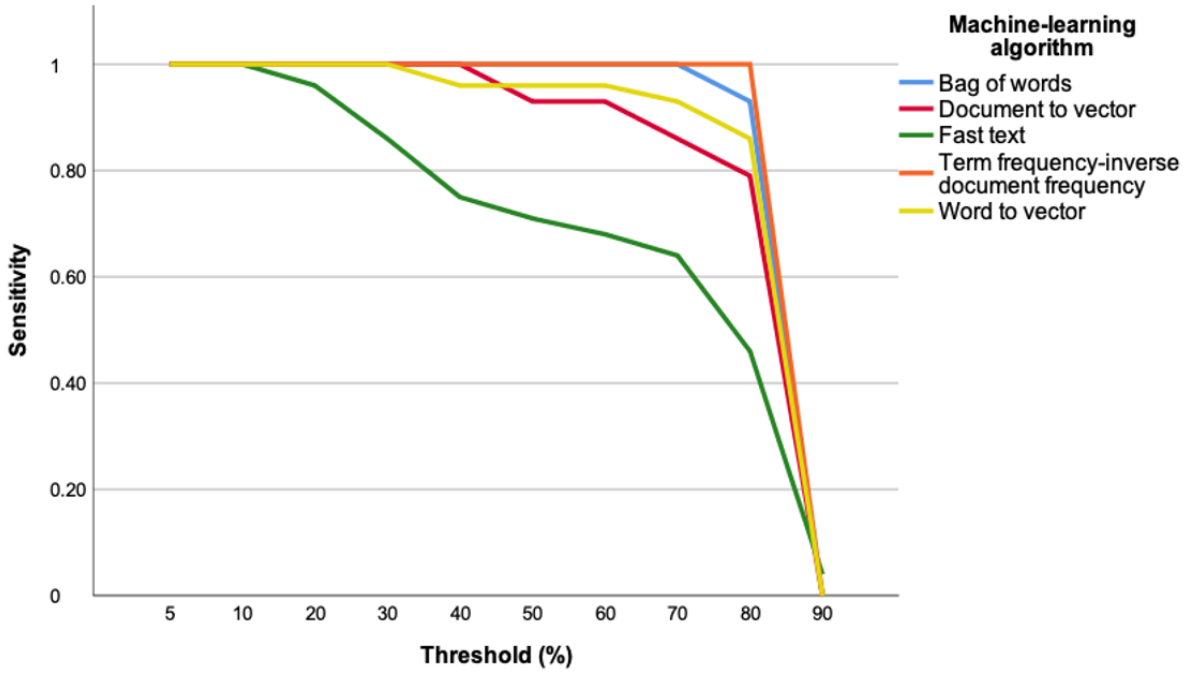
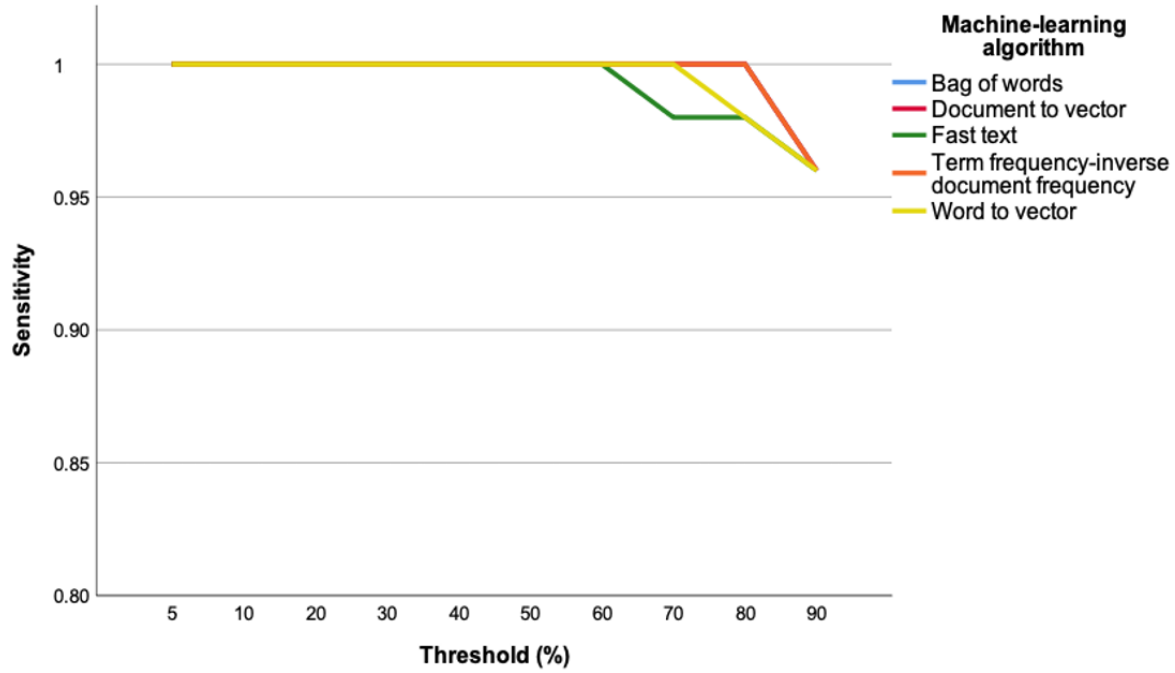


Figure 3. Machine learning algorithm training set performance (machine+one human reviewer citation assessment). The document to vector line overlaps with term frequency-inverse document frequency. The bag-of-words line overlaps with term frequency-inverse document frequency, demonstrating a sensitivity of 100% at a threshold of 80%.



Additional sensitivity analyses were performed using the bag of words and term frequency-inverse document frequency algorithms using a separate threshold for citations without an abstract (ie, title only) to evaluate whether these citations perform differently. For this analysis, the threshold for citations with an abstract was fixed at 70%, and the threshold for citations without an abstract varied among 30%, 50%, and 70%. The bag of words and term frequency-inverse document frequency algorithms demonstrated sensitivities of 100% for all dual threshold combinations (ie, 70/30, 70/50, and 70/70), both when citations were assessed by the ML algorithm alone or in combination with a single human reviewer.

We subsequently evaluated the bag of words and term frequency-inverse document frequency ML algorithms on a validation set of 2174 additional citations. Again, these citations were screened independently and in duplicate by crowd reviewers. The validation set included nine unique citations that met the inclusion criteria. On the basis of the sensitivity results from the training set, we chose to apply the following conservative thresholds to evaluate performance on the validation set: 70% for citations with an abstract and 50% for citations with title only. Both the bag of words and term frequency-inverse document frequency algorithms demonstrated a sensitivity of 92% when citations were assessed using the ML algorithm alone, and a sensitivity of 100% when used in combination with a single human reviewer.

In addition to sensitivity, we evaluated the specificity of the ML algorithm. Both the term frequency-inverse document frequency and bag of words algorithms demonstrated a similar specificity at 70% threshold (ie, 0.68), but the term frequency-inverse document frequency algorithm retained three fewer false positive citations. Given this marginally better performance, term frequency-inverse document frequency was selected as the final ML algorithm. Considering that ML algorithms are relatively novel in the conduct of large scoping reviews, we adopted a conservative approach to integrating the algorithm into citation screening for the remaining citations in the review. For citations with an abstract, the following three thresholds were selected:

1. Citations with a score ≥70% threshold were assessed by duplicate independent human assessment.
2. Citations with a score between 30% and 70% threshold were assessed by machine plus one independent human assessment.
3. Citations with a score ≤30% threshold were assessed by machine-only assessment.

For citations without an abstract (ie, title only), we adopted a conservative approach by selecting a 50% threshold and no option for machine-only citation assessment. Therefore, citations with a score ≥50% threshold were assessed by duplicate independent human assessment, and citations with a score <50% threshold were assessed by machine plus one independent human assessment.

Strengths and Limitations

This scoping review is the first phase of a larger research program to systematically evaluate children with CCI. To our knowledge, this scoping review is the first evidence synthesis to provide a systematic overview of the definitions used in the literature for identifying children with CCI and prolonged PICU admission. As such, the results of this review will be used to inform the development of a consensus case definition for pediatric CCI and set a priority agenda for future research. Defining pediatric CCI is an essential first step in understanding

the epidemiology of this high-risk PICU population, and a prerequisite for conducting future interventional and outcomes research. As the aims of this scoping review are descriptive and exploratory in nature, this preliminary study will identify the potential need to conduct a systematic review to address targeted and explanatory epidemiologic questions. This scoping review will also demonstrate the feasibility and validity of two innovative evidence synthesis methods, crowdsourcing and an ML algorithm, to execute a large scoping review.

This review has several important limitations. As the goal of this scoping review was to describe the definitions of pediatric CCI and prolonged PICU admission, it is limited to studies that explicitly identified and defined these concepts. This review will potentially miss records that did not use this specific language to define their population, and excluded studies that did not provide or reference a definition of pediatric CCI or prolonged PICU admission. Similarly, the study selection criteria in this review will exclude studies that focused only on the concept of prolonged technology use (eg, prolonged mechanical ventilation, prolonged extracorporeal membrane oxygenation). We seek to broadly understand pediatric CCI, and as a part of this objective, we will describe how the concept of organ support technology is applied in the published definitions of pediatric CCI.

Conclusions

This scoping review is the first, to the best of our knowledge, to (1) provide a systematic overview of the definitions used in the literature for identifying children with CCI and prolonged PICU admission and (2) describe the demographic and clinical characteristics of the populations historically defined in the pediatric CCI literature. This comprehensive literature review will evaluate existing or suggested definitions of pediatric CCI. In the absence of definitions, the review results will be used in future research to identify the key terms and constructs to inform the development of a working definition of pediatric CCI. Defining pediatric CCI is an essential first step in understanding the epidemiology of this high-risk PICU population and a prerequisite for conducting future interventional and outcomes research.

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Authors' Contributions

DJZ and KC conceived the idea for the scoping review. All authors contributed to the design of this review protocol. All authors participated in piloting and refining the search strategy, selection criteria, and data abstraction forms. DJZ drafted the paper. All authors read the paper, provided feedback, and approved the paper for submission. KC is the guarantor for this review.

Conflicts of Interest

None declared.

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Abbreviations

CCI: chronic critical illness
ML: machine learning
PICU: pediatric intensive care unit

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Protocol

Patient-Reported Benefits and Limitations of Mobile Health Technologies for Diabetes in Pregnancy: Protocol for a Scoping Review

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Abstract

Background: For women with pre-existing and gestational diabetes mellitus, pregnancy involves specialized and intensive medical care to improve maternal and infant outcomes. Medical management for patients with diabetes in pregnancy typically occurs via frequent face-to-face outpatient appointments. Barriers to face-to-face care during the COVID-19 pandemic have signaled the need for high-quality, patient-centered virtual health care modalities, such as mobile health (mHealth).

Objective: The objective of the proposed scoping review is to identify the patient-reported benefits and limitations of mHealth technology among women with diabetes in pregnancy. We also aim to determine how the women's experiences align with the best practice standards for patient-centered communication.

Methods: Arksey and O'Malley's framework for conducting scoping reviews with refinements by Levac et al will be used to guide the conduct of this scoping review. Relevant studies will be identified through comprehensive database searches of MEDLINE, Embase, Emcare, and PsycINFO. Following database searches, studies will be screened for eligibility at the title, abstract, and full-text level by two independent reviewers, with the inclusion of a third reviewer if required to reach consensus. Data charting of included studies will be conducted by one reviewer using a standardized data extraction form and verified independently by a second reviewer. Synthesis of results will be guided by Thomas and Harden's "Methods for the Thematic Synthesis of Qualitative Research in Systematic Reviews."

Results: As of August 2020, we have carried out the qualitative searches in the electronic databases MEDLINE, Embase, Emcare, and PsycINFO (Ovid interface) for a combined total of 8207 articles. Next, we plan to conduct the quantitative searches in the electronic databases MEDLINE, Embase, and Emcare (Ovid interface). We also plan to review the reference lists of relevant studies to identify additional eligible studies.

Conclusions: With the results of this review, we hope to describe the patient-reported benefits and limitations of mHealth technology for women with diabetes in pregnancy. Furthermore, we aim to determine how women's experiences align with the best practice standards for patient-centered communication. Ultimately, our review can provide valuable information for guideline developers, policy makers, and clinicians related to mobile technologies to support virtual care delivery for women with diabetes in pregnancy.

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KEYWORDS

diabetes; pregnancy; type 1 diabetes; type 2 diabetes; gestational diabetes mellitus; mobile health; mHealth; virtual care; scoping review

Introduction

Diabetes is estimated to affect 20.4 million births or 15.8% of pregnancies worldwide [1]. Of these, 83% of cases are attributed to gestational diabetes mellitus, with the remaining 17% due to type 1 and type 2 diabetes [1]. It is well-established that diabetes in pregnancy is associated with a significant risk of adverse pregnancy outcomes [1-4]. These include an increased risk of congenital anomalies, stillbirths, and infant death among pregnancies complicated by gestational and pre-existing diabetes compared to the background population [1-4]. There is also a high occurrence of premature delivery, birth injuries, need for neonatal intensive care, and maternal pre-eclampsia, as well as other complications among pregnancies affected by diabetes [1-4].

For women with both gestational and pre-existing diabetes, there is a strong inverse relationship between maternal glycemic control and adverse pregnancy outcomes [5,6]. A large multicountry study that included over 25,000 participants with gestational diabetes found a 5-fold increased risk of macrosomia among infants of mothers with fasting plasma glucose of 5.6-5.8 mmol/L compared to infants of mothers with fasting plasma glucose less than 4.2 mmol/L [5]. Among pregnant women with pre-existing diabetes, a systematic review found that, on average, there was a 3-fold increased risk of congenital anomalies, miscarriage, and perinatal mortality among expectant mothers with poor glycemic control compared to those with good glycemic control [6]. Additional studies have reported similar findings, strengthening the link between glycemic control during pregnancy and maternal and infant outcomes [7-11].

As the evidence indicates that improved glycemic control during pregnancy optimizes perinatal outcomes, expectant mothers with diabetes receive intensive and specialized care to achieve this goal. During pregnancy, women with diabetes attend approximately 15 face-to-face visits with health care providers [12]. These include appointments with obstetricians, endocrinologists, diabetes nurses, and dieticians, among others [12]. However, in early pregnancy, a time when the fetus is vulnerable to congenital anomalies [13], less than 15% and 40% of women with type 1 and type 2 diabetes achieve recommended glycemic targets, respectively [14]. Thus, even with intensive and specialized medical care, glycemic control remains suboptimal, contributing to adverse pregnancy outcomes among women with diabetes.

The COVID-19 pandemic has created a barrier to the frequent face-to-face appointments that characterize the medical management of diabetes in pregnancy, highlighting the need for virtual health care. Innovative approaches to virtual health care, such as mobile health (mHealth) technology that facilitates patient-provider communication, offer a promising option to support maternal and fetal well-being. Among nonpregnant adults with diabetes, mHealth interventions are associated with statistically significant and clinically important improvements in glycemic control [15] and there is the potential that mHealth could likewise contribute to improved glycemic control during pregnancy. Although virtual health care modalities, such as mHealth, provide promising options to support the management of chronic conditions, including diabetes in pregnancy, there may also be drawbacks to virtual health care delivery [16]. Marginalized groups in particular, such as patients with language barriers and those who lack access to technology, among others, may face significant challenges [16]. There may also be concerns regarding the quality of virtual health care delivery [16]. Thus, during this time of transition from face-to-face ambulatory care to virtual care, a focus on patient-centered, patient-provider communication is critical. According to King and Hoppe [17], best practice regarding patient-provider communication during medical encounters is communication that contributes to fostering the relationship, gathering information, providing information, making decisions, responding to emotions, and enabling disease- and treatment-related behaviors.

COVID-19 pandemic–induced limitations that impede face-to-face patient-provider communication may compromise the specialized and intensive care that supports expectant mothers with diabetes in achieving glycemic targets and optimizing pregnancy outcomes. It is possible that mHealth interventions that facilitate patient-provider communication may break down barriers and contribute to optimal glycemic control and pregnancy outcomes. These technologies ought to meet best practice standards for patient-centered communication. Therefore, the objective of this scoping review is to map the literature regarding patient-reported benefits and limitations of mHealth technologies that facilitate patient-provider communication in the context of diabetes in pregnancy. We will also determine how the women's experiences align with the best practice standards for patient-centered communication, as described by King and Hoppe [17].

Methods

Study Reporting and Registration

This scoping review protocol was preregistered with Open Science Framework (OSF) on March 25, 2021. Arksey and O'Malley's framework for conducting scoping reviews [18], with refinements by Levac et al [19] that provide recommendations and clarifications to the original framework, will be used to guide the conduct of this review. According to Arksey and O'Malley, scoping reviews can be conducted to achieve the following: (1) examine the extent, range, and nature of research activity; (2) determine the value for undertaking a full systematic review; (3) summarize and disseminate research findings; and (4) identify research gaps in the existing literature [18]. Scoping reviews allow researchers to incorporate a range of study designs and address questions beyond those related to intervention effectiveness [19]. This scoping review will align with Arksey and O'Malley's first and fourth scoping review

aims. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines will guide the reporting of the review [20].

Identifying the Research Question

The research question is twofold: (1) Among women with diabetes in pregnancy, what are the patient-reported benefits and limitations of mHealth technology? (2) How do the women's experiences align with the best practice standards for patient-centered communication?

Identifying Relevant Studies

Relevant studies will be identified by search strategies developed by health science librarians. First, we will search MEDLINE, Embase, Emcare, and PsycINFO for qualitative studies. Secondly, we will search for quantitative literature in MEDLINE, Embase, and Emcare. The reference lists of relevant studies will also be reviewed to identify additional eligible studies. Multimedia Appendix 1 provides the MEDLINE, Embase, Emcare, and PsycINFO search strategy for qualitative studies.

Study Selection

Following database searches, duplicates will be removed in EndNote and the remaining studies will be transferred to DistillerSR for the title and abstract screening and full-text review. Studies eligible for inclusion are primary studies that report benefits and limitations of mHealth technology used to support or facilitate virtual care for pregnant patients with gestational or pre-existing diabetes. Title and abstract screening will determine whether the study is about mHealth technology in pregnant women with gestational or pre-existing diabetes. The full-text review will determine whether the study elicits patient-reported benefits and/or limitations of mHealth technology. Title and abstract screening and full-text review will be conducted independently by two reviewers (KS and QRW). Any discrepancies will be resolved through discussion or by the inclusion of a third reviewer (DS).

Charting the Data

Data charting will be completed using a standardized data extraction tool. This tool will first be piloted to ensure accuracy and efficiency during the data charting process. Extracted data will include study characteristics, participant characteristics, and details regarding the described mHealth technologies. All text labelled "results" or "findings" in the included studies will also be extracted. Finally, relevant data will be extracted to determine how the women's experiences align with King and Hoppe's best practice standards for patient-centered communication [17]. Data extraction will be conducted by one reviewer (KS) and verified independently by a second reviewer (QRW). Any discrepancies will be resolved through discussion or by the inclusion of a third reviewer (DS).

Collating, Summarizing, and Reporting the Results

The approach to data synthesis will be adapted from Thomas and Harden's "Methods for the Thematic Synthesis of Qualitative Research in Systematic Reviews" [21]. This method involves the extraction of all text labelled "results" or "findings" in included studies. The extracted text will be entered verbatim into NVivo. Following the transfer of the text to NVivo, three stages of thematic analysis will be conducted as follows: (1) free line-by-line coding of the study findings; (2) organization of free codes into descriptive themes; and (3) development of analytical themes [21].

Results

As of August 2020, we have completed the qualitative search strategy. We carried out the qualitative searches in the electronic databases MEDLINE, Embase, Emcare, and PsycINFO (Ovid interface) for a combined total of 8207 articles. Next, we plan to conduct the quantitative searches in the electronic databases MEDLINE, Embase, and Emcare (Ovid interface). We also plan to review the reference lists of relevant studies to identify additional eligible studies. Multimedia Appendix 1 provides the MEDLINE, Embase, Emcare, and PsycINFO (Ovid interface) search strategies for qualitative studies.

Discussion

For women with diabetes, pregnancy is a critical period that requires intensive and specialized medical management to optimize perinatal outcomes. Among nonpregnant adults with diabetes, mHealth interventions have been shown to improve glycemic control [15]. In the context of COVID-19 pandemic–induced shifts from ambulatory to virtual care delivery, mHealth interventions that enable and support patient-provider communication may potentially serve as a means of improving glycemic control and pregnancy outcomes. However, concerns regarding the quality of virtual health care delivery [16] signal the need for an emphasis on patient-provider communication that is patient-centered. The proposed review will aim to describe the patient-reported benefits and limitations of mHealth technology among women with diabetes in pregnancy and determine how women's experiences align with the best practice standards for patient-centered communication. The results of this review will be disseminated through peer-reviewed journals and conference presentations to engage relevant stakeholders, including patient-partners, clinicians, researchers and technology developers, and policy makers who are involved in the medical management of women with diabetes in pregnancy.

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Authors' Contributions

KS drafted the manuscript. KS, QRW, HTM, DFL, and DS contributed to the design of the review protocol. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Qualitative search strategy for Ovid MEDLINE, Embase, Emcare, and PsycINFO.
[DOCX File , 15 KB - resprot_v10i10e29727_app1.docx]

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Abbreviations

mHealth: mobile health
OSF: Open Science Framework
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Health Care Professionals' Experiences and Perspectives on Using Telehealth for Home-Based Palliative Care: Protocol for a Scoping Review

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Abstract

Background: Telehealth seems feasible for use in home-based palliative care. However, acceptance among health care professionals (HCPs) is essential for the successful delivery of telehealth in practice. No scoping review has mapped the experiences and perspectives of HCPs on the use of telehealth for home-based palliative care.

Objective: The aim of this review is to systematically map published studies on HCPs' experiences and perspectives on the use of telehealth in home-based palliative care.

Methods: The proposed scoping review will employ the methodology of Arksey and O'Malley. This protocol is guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P). A systematic search will be performed in MEDLINE, PsycINFO, EMBASE, CINAHL, Allied and Complementary Medicine (AMED), and Web of Science for studies published between January 2000 and July 5, 2021. We will also hand search the reference lists of included papers to identify additional studies of relevance. The search will be updated in 2022. Pairs of authors will independently assess the eligibility of studies and extract data. The first 2 stages of thematic synthesis will be used to thematically organize the data. Because the scoping review methodology consists of reviewing and collecting data from publicly available materials, this study does not require ethics approval.

Results: The database searches; testing of eligibility criteria; and screening of titles, abstracts, and full-text papers will be performed by fall 2021. The results from this scoping review will be presented as a descriptive summary of the results from all included papers, and will be inductively organized into descriptive themes. A frequency table illustrating which papers were included in which descriptive themes will be made. Results are anticipated by the fall of 2022.

Conclusions: A mapping of studies could identify research gaps regarding HCPs' experiences and perspectives on the use of telehealth in home-based palliative care and may determine the value and feasibility of conducting a full systematic review.

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KEYWORDS

health care technology; home care services; palliative care; review; telehealth; telemedicine

Introduction

More people will require palliative care in the future due to the growing number of older people and the increasing prevalence of chronic illnesses [1,2]. Palliative care is an approach that aims to improve the quality of life of patients and their families facing life-threatening illness. Palliative care is applicable early in the course of illness, in conjunction with treatments that intend to prolong life [3]. Palliative care is relevant for various diseases and conditions such as cancer, dementia, chronic lung diseases, and heart diseases [4]. Most patients receiving palliative care prefer to be cared for and spend as much time as possible in their own homes [5,6]. Home-based palliative care is associated with a reduction in symptom burden and increased patient and caregiver satisfaction [7]. A key goal in palliative care is to enable patients to spend more time at home by providing access to coordinated, continuous, and specialized palliative care at home [8]. However, many patients experience that the palliative care trajectory is unpredictable, and complaints about uncoordinated care, unmet palliative care needs at home, lack of regular communication with both health care professionals (HCPs) and between specialist and home care professionals are common [9,10].

The recent and ongoing COVID-19 pandemic presents additional challenges for HCPs in providing home-based palliative care. Physical distancing requirements, lockdowns, and lack of personal protective equipment may limit the access to home-based palliative care. Subsequently, increased isolation and suffering may increase the care burden on the families and caregivers [11].

Telehealth is increasingly used in home care and is defined "as the provision of healthcare remotely by means of a variety of telecommunication tools" [12]. A scoping review [13] suggests that telehealth is feasible for use in home-based palliative care as it improves access to palliative care at home, promotes self-monitoring, and enhances patients' feelings of security and safety [13]. There is a significant increase in health care costs in the final years of life [14], and it is expected that telehealth solutions may contribute to more efficient use of resources in palliative care by preventing and reducing hospital admissions, emergency department attendances, and deaths in hospitals [15-17]. It may also enhance collaboration between different health care services by improving the information flow [17,18]. Recent policy changes during the COVID-19 pandemic have reduced barriers to implement telehealth services and have promoted the use of telehealth in palliative care as a way to improve communication between isolated patients and their families, and between patients and HCPs [19,20].

Although the possibilities within telehealth appear promising in facilitating high-quality care for various conditions, many HCPs feel that technology is inappropriate for the palliative care population due to age, burden of illness, and rapidity of deterioration [16]. The most common fear of technology is that machines will replace all human contact [21]. Previous studies have shown that HCPs may characterize palliative care as high touch rather than high tech and concerns about telehealth being burdensome for the patients may limit their interest in implementing and applying telehealth solutions [22,23]. Further, reduced face-to-face contact with patients and lack of acceptance of this way of working among HCPs seem to be barriers in implementing telehealth in palliative care [24].

Previous literature reviews regarding the use of telehealth in palliative care have primarily examined patient or caregiver outcomes and experiences [13,17,23,25] or have focused on elderly patients, patients with chronic conditions [26,27], or children in need of palliative care [28,29].

Bienfait et al [22] published a systematic review regarding HCPs' perceptions of using telehealth for monitoring patients with chronic disease and how those findings could transpose to palliative care. Another systematic review examined the use of video consultations in general and specialized palliative care to various patient groups from the perspectives of patients, caregivers, and HCPs [30]. They found that HCPs were positive toward the use of video consultations in palliative care, but expressed concerns regarding technical challenges, increased workload, and the required additional training in how to conduct video consultations. A systematic review [31] examined the use of technology for communication in palliative care from the perspectives of HCPs, patients, and caregivers. They found that the use of technology for communication efficiency resulted in improved quality of care and communication, and reduction of documentation efforts and overall health care costs. However, they did not report nor investigated HCPs' experiences or perspectives of utilizing technology apps in home-based palliative care [31].

With the emergence of new research regarding the use of telehealth in palliative care, there is a need for a comprehensive review of the existing literature on how HCPs experience and perceive the use of telehealth to deliver home-based palliative care. Identifying facilitators and barriers for implementation of telehealth among HCPs is important, as acceptance of this way of working is essential to the successful delivery of telehealth in practice [32]. In line with the recommendations of Arksey and O'Malley [33], we have chosen to conduct a scoping review, as this allows the inclusion of studies with different study designs and is suitable to describe findings and range of studies within the field of telehealth. A mapping of studies could also identify research gaps regarding telehealth in palliative care and may determine the value and feasibility of conducting a full systematic review. Further, a scoping review may also be suitable to more accurately define a research question for a

systematic review [33] and is also suitable to bringing together literature in disciplines with emerging evidence [34]. To the best of our knowledge, no scoping review has targeted the experiences and perspectives of HCPs on the use of telehealth for home-based palliative care. Consequently, the aim of this scoping review is a systematic mapping of published studies on the use of telehealth in home-based palliative care with focus on experiences and perspectives of HCPs. The research question is: What is known from published studies about HCPs' experiences and perspectives on using telehealth for home-based palliative care?

Methods

Overview

Scoping reviews begin with the development of a protocol that aims to predefine the objectives and methods of the scoping review and detail the proposed plan. Because of the more iterative nature of a scoping review in contrast to a systematic review, some deviations from the protocol may be necessary [34]. This scoping review will employ the methodology of Arksey and O'Malley [33], which consist of the following stages: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. The reporting of this protocol is guided by the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) [35], while the reporting of the upcoming scoping review will be guided by the PRISMA extension for scoping reviews (PRISMA-ScR) [36].

Eligibility Criteria

The inclusion and exclusion criteria are shown in Table 1. The first and last author will independently test the inclusion and exclusion criteria on the same 5% of the retrieved studies to assess the robustness of the criteria in capturing relevant publications. The inclusion and exclusion criteria may be revised based on conflicts during or after this initial testing. Once the final set of criteria is agreed upon, the entire group of researchers will screen the remaining titles and abstracts. The language criteria are based on authors' fluency in the included languages.

Table 1. Inclusion and exclusion criteria.

Criterion	Inclusion	Exclusion
Types of studies	Qualitative, quantitative, or mixed methods studies.	Any type of review, case report, letter, book chapter, guideline, comment, discussion, editorial, conference abstract, study protocol, master's thesis, or PhD thesis.
Period	January 1, 2000, until the updated search.	Before January 1, 2000, and after the updated search.
Language	English, Chinese, Portuguese, Spanish, Norwegian, Swedish, or Danish.	All other languages.
Type of participants	Papers including HCPs[a] using telehealth with patients in home-based palliative care.	Papers including HCPs using telehealth with patients outside of a palliative care environment, those that only tend to family caregivers, or studies that do not present data from the perspective of HCPs.
Phenomenon of interest	HCPs' experiences of and perspectives on the use of telehealth in home-based palliative care.	HCPs' experiences of and perspectives on the use of telehealth at home without interaction with the patient, or experience of use of telehealth in hospital, nursing home, or hospice. Telehealth including only telephone follow-up.

[a]HCP: health care professional.

Information Sources

We aim to perform a systematic search in the following electronic databases: MEDLINE, PsycINFO, EMBASE, CINAHL, Allied and Complementary Medicine (AMED), and Web of Science.

Search Strategy

The search strategy in MEDLINE (Multimedia Appendix 1) will be built by an experienced research librarian (KM) and 2 of the other authors (EL and SS) using MeSH terms and text words. The search will consist of 3 elements: (1) palliative care, (2) telehealth, and (3) home setting. The search strategy will be piloted to validate appropriateness of text words and MeSH terms, and will be peer reviewed by a second experienced research librarian (MAØ), using the Peer Review of Electronic Search Strategies checklist [37]. The search strategy will then be adopted for each database. The database searches will be updated 2 months prior to publication. We will also hand search the reference lists of included papers to identify additional studies of relevance.

Data Management

The research librarian will upload the publications identified in the searches to EndNote for removal of duplicates and transfer the publications into the web application Covidence [38] to facilitate independent selection of eligible publications, as well as storage.

Selection Process

Pairs of authors will independently screen titles, abstracts, and full-text papers to determine their eligibility. EL and SS will solve potential conflicts among the pairs based on consensus. The study selection process will be reported using the PRISMA flowchart [39], alongside the reasons for exclusion of full-text publications.

Data Collection Process

A standardized data charting form in Covidence will be developed and used to chart relevant data from the included papers. The following data may be included: authors, publication year, country, aim, sample, telehealth solution, design, and results related to the research question. The data charting form will be reviewed by the entire research team and pilot tested by the first and last author on 5 studies to ensure that the form is capturing the information accurately. More studies may be piloted based on the number of included studies. Based on these experiences, the data charting form may be revised. Pairs of authors (EL/SS, AN/HH, WC/AW, CB/EL, NJ/HT, and SS/OD) will conduct the data charting. One author will extract data, while the other author will check accuracy. Any discrepancies will be further discussed among the pairs of authors and agreement will be based on consensus or the involvement of the first and last author.

Risk of Bias and Quality Appraisal

A key difference between scoping reviews and systematic reviews is that the former is not intended to be used to critically appraise or assess the risk of bias of a cumulative body of evidence. Generally, scoping reviews aim to provide an overview of existing literature regardless of methodological rigor or risk of bias [36]. Therefore, the included sources of evidence in this review will not be assessed for risk of bias or methodological quality. This is in line with the framework of Arksey and O'Malley [33] and Tricco et al [36].

Data Synthesis

A scoping review seeks to provide an overview of the data rather than synthesize the evidence like that in a systematic review. However, a scoping review still needs an analytic framework to present a narrative account of the data [33]. We will use the first 2 stages of thematic synthesis [40] to inductively organize our data. In stage 1 of the thematic synthesis, the data from the result section of the included studies will be read multiple times and line-by-line coding will be applied to identify patterns, similarities, and differences in the experiences and perspectives of HCPs on the use of various technological solutions in home-based palliative care. In stage 2, the codes will be compared for similarities and differences and organized into descriptive themes with low degree of abstraction and interpretation. The first, second, third, and last author will organize the data. The final descriptive themes will be determined by the authors through discussion and consensus among all the authors. The qualitative data analysis software NVivo (QSR International) [41] will be used to organize the data. The codes and the descriptive themes will be discussed with all members of the research team who have diverse research and clinical expertise regarding telehealth, palliative care, and chronic illness. This could enhance the trustworthiness of the results.

Results

In a scoping review, the results may be presented in a logical, diagrammatic, or tabular form, or in a descriptive format that aligns with the objectives of the review [34]. The results from this scoping review will be presented as a descriptive summary of the results from all included papers, and will be inductively organized into descriptive themes. A frequency table illustrating which papers were included in which descriptive themes will be made. A figure illustrating the hierarchical coding tree may also be developed to further illustrate the results [39].

Discussion

We introduced the rationale and design of a scoping review to answer our research question: "What is known from published studies about HCPs' experiences and perspectives on using telehealth for home-based palliative care?". Research indicates that telehealth is feasible for use in palliative care [13], may increase patient and caregiver satisfaction, and may contribute to increased resource efficiency in home-based palliative care [15-17]. However, research also indicates that HCPs may be a key barrier in implementing technology, and that acceptance of this way of working among HCPs is vital for the successful implementation of telehealth in practice [32]. This scoping review will be important to provide an overview on published studies on HCPs' experiences and perspectives on the use of telehealth in home-based palliative care. This review may identify gaps in the existing literature and determine whether a full systematic review is feasible. Furthermore, this review could provide a deeper understanding of HCPs' perspectives and experience in telehealth in home-based palliative care. This may aid policy makers and telehealth developers in designing user-centric, demand-driven telehealth solutions. Because the scoping review methodology consists of reviewing and collecting data from publicly available materials, this study does not require ethics approval.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Medline search strategy.
[PDF File (Adobe PDF File), 74 KB - resprot_v10i10e33305_app1.pdf]

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Abbreviations

HCP: health care professional
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol
PRISMA-ScR: PRISMA extension for scoping reviews

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