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Protocol

Evaluation of a Health Information Technology–Enabled Collective Intelligence Platform to Improve Diagnosis in Primary Care and Urgent Care Settings: Protocol for a Pragmatic Randomized Controlled Trial

Valy Fontil[1,2], MD, MAS; Elaine C Khoong[1], MD, MS; Mekhala Hoskote[1,2], BA; Kate Radcliffe[1,2], BA; Neda Ratanawongsa[1,2], MD, MPH; Courtney Rees Lyles[1,2], PhD; Urmimala Sarkar[1,2], MD, MPH

[1]Division of General Internal Medicine, University of California San Francisco, San Francisco, CA, United States
[2]UCSF Center for Vulnerable Populations, University of California San Francisco, San Francisco, CA, United States

Corresponding Author:
Valy Fontil, MD, MAS
Division of General Internal Medicine
University of California San Francisco
1001 Potrero Avenue
Building 10, Ward 13
San Francisco, CA, 94143
United States
Phone: 1 415 206 4087
Email: valy.fontil@ucsf.edu

Abstract

Background: Diagnostic error in ambulatory care, a frequent cause of preventable harm, may be mitigated using the collective intelligence of multiple clinicians. The National Academy of Medicine has identified enhanced clinician collaboration and digital tools as a means to improve the diagnostic process.

Objective: This study aims to assess the efficacy of a collective intelligence output to improve diagnostic confidence and accuracy in ambulatory care cases (from primary care and urgent care clinic visits) with diagnostic uncertainty.

Methods: This is a pragmatic randomized controlled trial of using collective intelligence in cases with diagnostic uncertainty from clinicians at primary care and urgent care clinics in 2 health care systems in San Francisco. Real-life cases, identified for having an element of diagnostic uncertainty, will be entered into a collective intelligence digital platform to acquire collective intelligence from at least 5 clinician *contributors* on the platform. Cases will be randomized to an intervention group (where clinicians will view the collective intelligence output) or control (where clinicians will not view the collective intelligence output). Clinicians will complete a postvisit questionnaire that assesses their diagnostic confidence for each case; in the intervention cases, clinicians will complete the questionnaire after reviewing the collective intelligence output for the case. Using logistic regression accounting for clinician clustering, we will compare the primary outcome of diagnostic confidence and the secondary outcome of *time with diagnosis* (the time it takes for a clinician to reach a diagnosis), for intervention versus control cases. We will also assess the usability and satisfaction with the digital tool using measures adapted from the Technology Acceptance Model and Net Promoter Score.

Results: We have recruited 32 out of our recruitment goal of 33 participants. This study is funded until May 2020 and is approved by the University of California San Francisco Institutional Review Board until January 2020. We have completed data collection as of June 2019 and will complete our proposed analysis by December 2019.

Conclusions: This study will determine if the use of a digital platform for collective intelligence is acceptable, useful, and efficacious in improving diagnostic confidence and accuracy in outpatient cases with diagnostic uncertainty. If shown to be valuable in improving clinicians' diagnostic process, this type of digital tool may be one of the first innovations used for reducing diagnostic errors in outpatient care. The findings of this study may provide a path forward for improving the diagnostic process.

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KEYWORDS

decision support systems, clinical diagnosis; medical informatics

Introduction

Background

Diagnostic errors (defined as missed, delayed, or wrong diagnoses) in primary care affect an estimated 1 in 20 US adults every year [1]. About half of these errors can lead to serious preventable harm, but few interventions have been developed and tested to reduce diagnostic errors in real-world ambulatory care settings such as primary care or urgent care clinics [1-4]. This significant gap in clinical practice carries tremendous public health implications. Most individuals receive care in ambulatory care settings [5]. Diagnosis is particularly challenging in primary and urgent care because of 2 structural factors: (1) the short time duration and pressure to complete visits affects cognition and (2) primary care encompasses the broadest range of clinical concerns, from common diseases to rare conditions [6].

In current usual practice, clinicians at primary care and urgent care clinics commonly diagnose patients independently without collaboration or consultation with other health professionals or the use of health information technology (IT), potentially leading to an increased risk of diagnostic errors [7]. In focus groups about outpatient diagnosis, clinicians identified the use of technology to improve communication among them as a key strategy to enhance timely and accurate diagnosis [8]. In its recent report on diagnostic error, the National Academy of Medicine suggested that health systems employ 2 key strategies that are essential to reducing diagnostic error in the ambulatory care setting: (1) enhance interclinician collaboration and (2) develop and utilize health IT innovations in the diagnostic process [6]. A collective intelligence technology platform could be a promising tool to implement these 2 key strategies.

Collective intelligence is defined as shared or group intelligence that emerges from the collaboration or collective efforts of many individuals. It harnesses the ability of a group to outperform the individual in a variety of cognitive tasks [7]. IT platforms offer the opportunity to connect people and harness their collective intelligence through crowdsourcing—the practice of obtaining input into a task or project by enlisting the services of a large number of people via the internet [9]. In discrete tasks related to medical decision making, such as classification of radiology scans and pathological specimens, collective intelligence technology has been shown to improve accuracy when compared with individual decision making [10,11]. However, the impact of collective intelligence technology on diagnostic accuracy remains unproven in outpatient practice. Studies examining collective intelligence technologies have shown that users are enthusiastic about cross-discipline collaboration and easily obtaining expert feedback but wary of inaccuracies and inefficiency of using a collective intelligence tool [12].

In previous simulation testing, the collectively derived output from a collective intelligence platform outperformed its individual physicians in identifying the correct diagnosis in its assessment of standardized clinical cases [13,14]. However, effective implementation of such a tool in the outpatient setting requires examination of its efficacy and usability in real-world primary care and urgent care clinics.

Study Objectives

In this pragmatic randomized controlled trial, we will examine the efficacy of a collective intelligence technology platform on improving primary clinicians' confidence in their diagnostic assessments and their accuracy in making a correct diagnosis. We will also examine clinicians' perceptions of the usability of the collective intelligence technology platform and their likelihood of using (ie , intention to use) such a platform in routine primary care or urgent care practice to assist with the diagnostic process.

Ethical Approval

This study was reviewed and approved by the institutional review board at the University of California, San Francisco.

Methods

Setting and Study Population

We will use a convenience sampling approach to recruit primary care and urgent care clinicians in San Francisco, including clinicians from University of California San Francisco (UCSF) primary care clinics and San Francisco Department of Public Health (SFDPH) health care system, which includes 12 urban safety-net primary care clinics that serve a low-income and racially and ethnically diverse patient population. This system is an integrated care system with primary care clinics throughout the city of San Francisco, including 2 academic clinics that are staffed by UCSF faculty physicians. The clinics also provide urgent care through clinic sessions (half days or entire days) reserved for urgent care visits.

Intervention

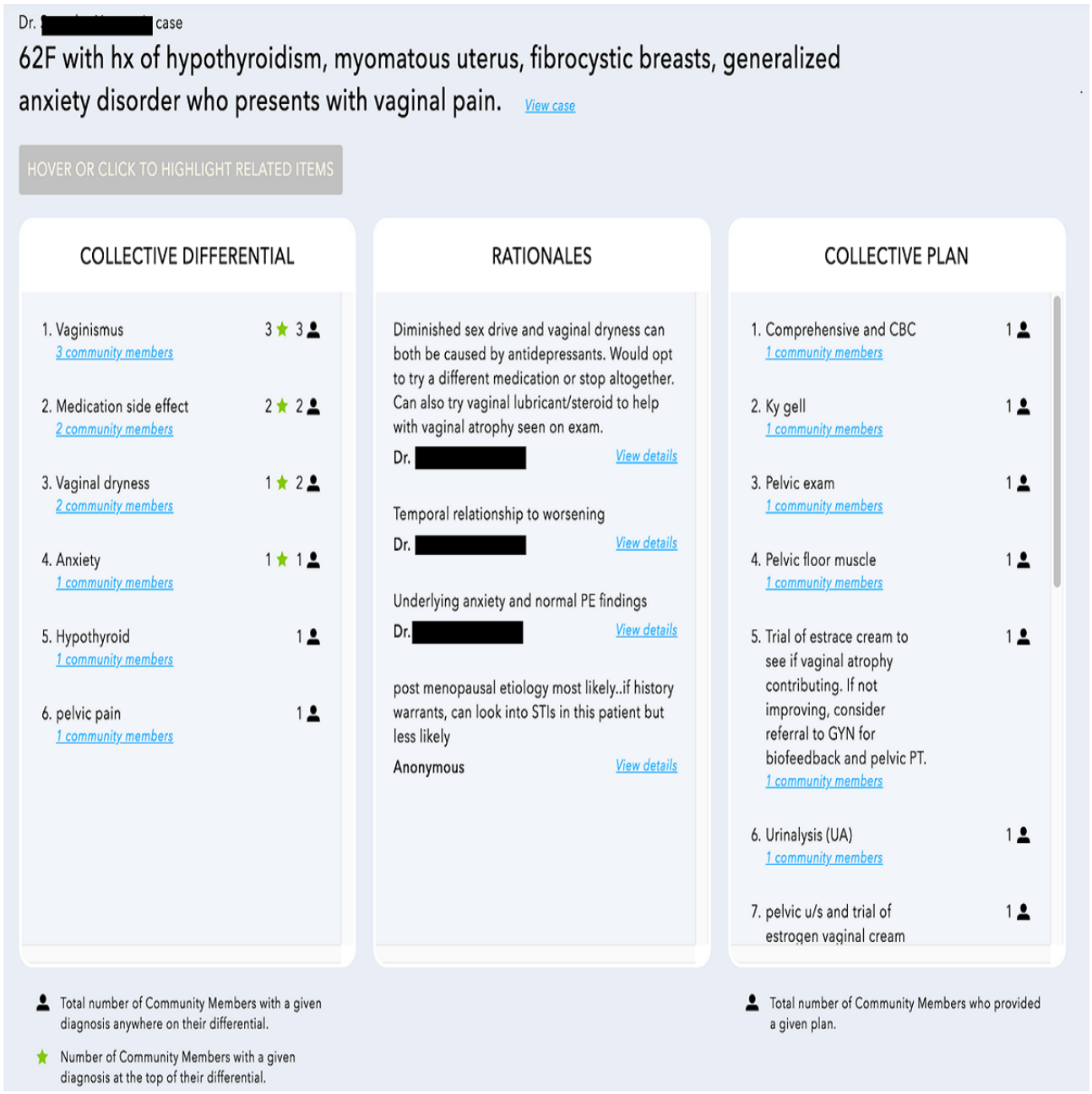
The intervention in this study is the provision of a Web-based collective intelligence output to primary care clinicians within 80 hours of a case presentation to assist them in the diagnostic process for routine clinical cases that do not yet have an established, confirmed diagnosis.

Collective Intelligence Platform

The Human Diagnosis Project (Human Dx) is a Web-based and mobile collective intelligence platform designed to implement both key strategies for reducing diagnostic error recommended by the National Academy of Medicine—interclinician collaboration and use of health IT in the diagnostic process—by utilizing collective intelligence among clinicians. Clinicians input the relevant details of a clinical case or question into the Human Dx platform. Afterward, any number of clinicians (including peers and specialists) participating on the platform, a minimum of 5 for this study, independently review the case and provide their own differential diagnoses and management plans. Using advanced techniques including prefixed search,

autocomplete, and natural language understanding, Human Dx is able to structure clinicians' clinical assessments and aggregate them to produce collective intelligence [13]. The collective intelligence output consists of (1) a collective differential diagnosis derived from a synthesis of respondents' differential diagnoses, (2) a collective management plan derived from a synthesis of respondents' management plans, and (3) free-text explanations from respondents of the rationales behind their differential diagnoses and plans (Figure 1). Human Dx has been available since 2014 and has over 21,000 physician and medical student users who have solved or entered at least one case. To date, there are over 282,000 entered or solved cases on the platform.

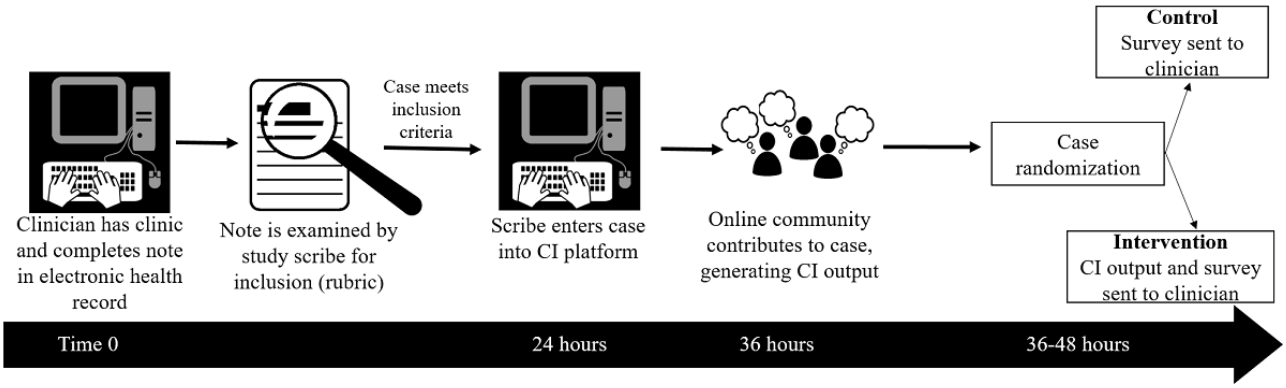
Figure 1. Screenshot of a collective intelligence output from the Human Dx platform for a clinical case. The columns display the collective intelligence output with the differential diagnosis, plan, and rationales. The interface is interactive – users can hover or click to see details of the case that was entered and details on the output differential diagnosis, rationales, and plan.



Study Design

This is a pragmatic randomized controlled trial in which primary care clinicians are followed over 4 to 8 weeks to identify a minimum of 20 cases, for each clinician, with potential diagnostic uncertainty. Half of the selected cases for each clinician will be randomized to the intervention and the clinician will receive a collective intelligence output for those cases. Human Dx will generate collective intelligence for the remaining (control) cases, but clinicians will not receive the collective intelligence output for these cases (Figure 2).

Figure 2. Workflow for participants. At baseline clinicians complete their normally-scheduled clinical sessions and complete their notes in the electronic health record. A study scribe examines each note and determines inclusion based on a study rubric. The study scribe enters the case into the collective intelligence (CI) platform within 24 hours and online contributors provide their own assessments to generate a CI within 36 hours. The CI output is sent to the study team, who randomize each case, and send the CI output to participants for cases randomized to the intervention. Participants receive a post visit questionnaire for all study cases (intervention and control).



Selection, Entry, and Randomization of Clinical Cases

For the purpose of this study, clinicians will not enter their own cases. For case entry, we will utilize study scribes who are medical doctors (MD) in their second or third year of internal medicine residency at UCSF. These scribes are analogous to intended real-world users of the Human Dx platform (ie, primary care and urgent care medical providers). On the basis of each participant's clinical schedule, study scribes will access the electronic health record within 24 to 36 hours after the participant's clinic session and identify cases that meet the study selection criteria (see below).

Study scribes enter cases that meet the inclusion criteria into the collective intelligence platform. A minimum of 5 clinicians will act as *contributors* who review and comment on each case in the collective intelligence platform within 24 to 36 hours of case entry, generating a collective intelligence output. The contributors recruited by Human Dx for this study were US-based attending-level physicians in internal medicine or family medicine. They were recruited from an existing pool of active Human Dx users (ie, they had solved at least one case within 3 months of being recruited for the study), which does not include any of the clinician participants in our study population. They are not affiliated with our study team and are blinded to our study procedures including case randomization (Figure 2).

Once the collective intelligence output becomes available for a case, the study team randomizes it to the intervention or control cases. The study team assigned each case a unique study identification number for tracking purposes. Using a random number generator in blocks of four, we will randomize half of the cases, for each clinician, to an intervention group in which the clinician will receive a collective intelligence output between 60 and 80 hours from the time the clinician saw the patient in the clinic (ie, within 24-36 hours of case entry). For cases randomized to the controlled group, Human Dx will generate collective intelligence, but it will not be shared with the clinician. Clinicians will complete an online postvisit questionnaire for all of their cases (control and intervention) that provides their initial impressions of the case (eg, differential diagnosis and perceived case difficulty) and level of diagnostic confidence. The questionnaire for cases assigned to the intervention group includes additional questions that the clinician will answer after reviewing the collective intelligence output to assess the effect of the output on their diagnosis, plan, and confidence. The study scribes and the *contributors* on Human Dx will be blinded to case randomization.

Case Selection Criteria

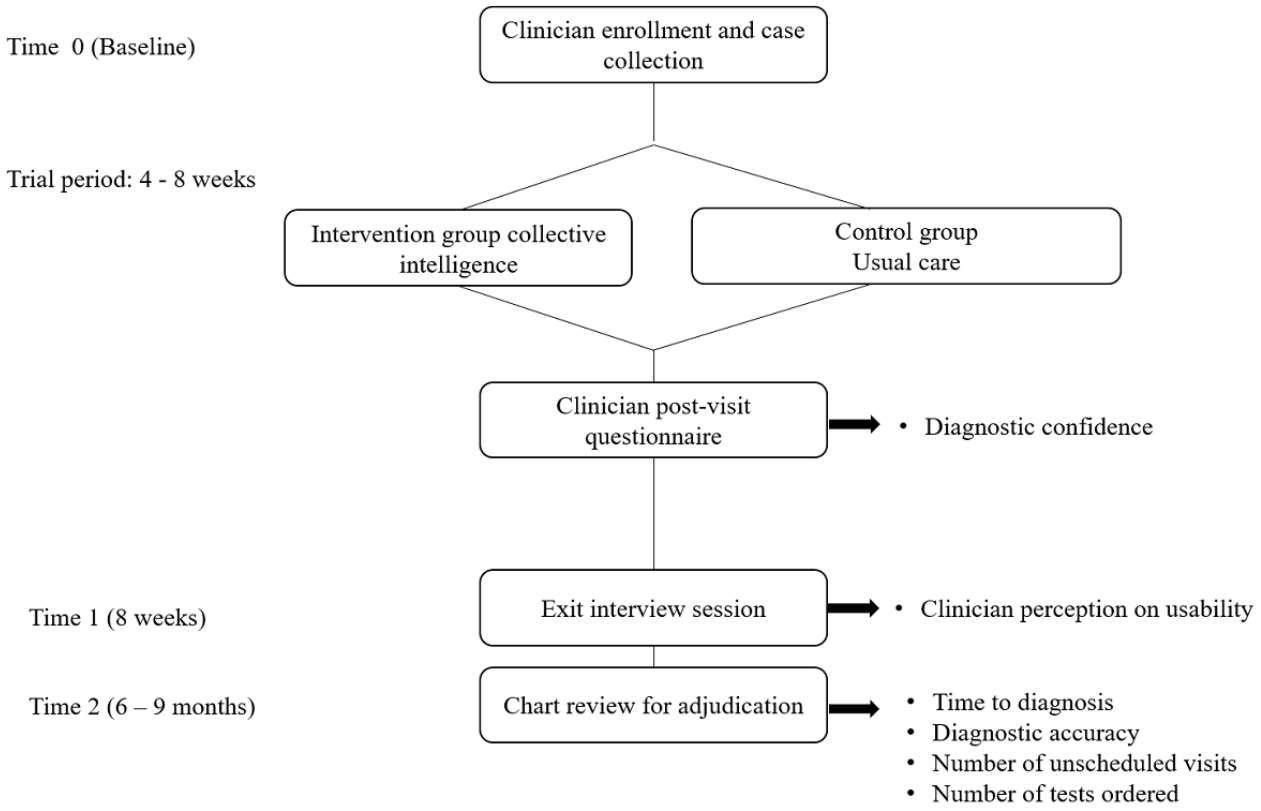
Scribes will select cases based on a rubric designed to capture diagnostic uncertainty. If a case meets any of the following criteria, it will be entered into the Human Dx platform: (1) a new symptom or abnormality in laboratory, physical exam, or radiographic finding; (2) a recurrent symptom or abnormality in laboratory, physical exam, or radiographic finding without a clear diagnosis or etiology; (3) a pending diagnostic test ordered to evaluate a new or unresolved condition; (4) empiric treatment provided without complete diagnostic certainty; and (5) if the clinician submitted a request for electronic consultation from a specialist within the health network for a diagnostic or management problem. Clinicians may also flag a case for review that the scribes will enter into the Human Dx platform whether or not it meets the above rubric's selection criteria.

Data Collection and Study Procedures

Study Period

We will follow participants' consecutive clinic sessions over a period of 4 to 8 weeks to select a minimum of 20 cases per clinician. After all postvisit questionnaires are completed, the participant will participate in a 1-hour exit interview including an in-person survey and semistructured interview to assess the efficacy and usability of collective intelligence for medical diagnosis from the perspective of primary care and urgent care clinicians (Figure 3).

Figure 3. Study procedures. At baseline, clinicians are recruited and cases are collected and randomized to the intervention and control groups. Post-visit questionnaires will assess diagnostic confidence (the primary outcome) for each case. Exit interview sessions at 8 weeks will explore clinicians' perception on usability. At 6-9 months, will conduct electronic medical record review to adjudicate clinic outcomes (secondary and exploratory outcomes).



Postvisit Questionnaires

For cases randomized to the control group, a research assistant will email the study participant a brief one-line description of the case accompanied with instructions to fill an online postvisit questionnaire (Multimedia Appendix 1) that captures the participant's clinical thinking. The brief one-line description is important to alert the participant to which case the questionnaire is referring; we will keep each one-line description in the study's records to act as a case identifier. For cases randomized to the intervention, the participants will receive instructions to complete an online questionnaire in similar fashion as described above for the control cases. In addition, we will provide the participant a Web link to access the collective intelligence output for the intervention case as well as the questionnaire that will assess the impact of the collective intelligence on their clinical thinking (eg, confidence and decision making; see Multimedia Appendix 1). All instructions to participants will be sent as a single email. Participants will be instructed in the email to review the collective intelligence output for intervention cases only when prompted, to ensure that they respond to survey questions designed to assess their initial clinical thinking (for both intervention and control cases) before reviewing the collective intelligence output that will be available only for intervention cases.

Exit Survey and Interview

We will conduct an exit session to complete an in-person exit survey and semistructured interview with at least 6 participants from each health system (UCSF and SFDPH) for a minimum total of 12 and continue interviewing more participants (if needed) until we reach thematic saturation. Previous studies have suggested a small sample (N=10) can collect most of the salient ideas from semistructured interviews with basic elements for meta-themes emerging after just 6 interviews [15,16]. After we reach thematic saturation, we will stop conducting in-person interviews, but we will email Web links to the online exit survey to all remaining participants not invited for in-person interviews. The first part of the exit survey will collect data on clinician factors such as professional degree (MD vs nurse practitioner [NP]), years of practice, and medical specialty (family medicine vs internal medicine). We used a modified Technology Acceptance Model (TAM) framework to inform construction of the semistructured interview guide and the second part of the survey. TAM is a validated theory of technology acceptance that has been widely used outside of health care and has become an important theoretical tool for health IT research [17]. As a theory, TAM suggests perceived usefulness (PU) and perceived ease-of-use (PEU) as the 2 major factors that influence how users come to accept and use a technology. Our survey will also measure participants' willingness or intention to use the collective intelligence platform beyond this study period—the interview guide will explore perceived barriers and facilitators that could influence their willingness to use. In addition to these concepts, our interview guide also includes additional constructs such as general satisfaction, trust, and system facilitators as well as supplemental open-ended questions to allow free expression of ideas. We will also ask participants to provide suggestions about the visual and content display of the platform output (see

Multimedia Appendices 2 and 3 for contents of the exit survey and interview guide).

Outcomes and Measurements

Primary and Secondary Outcomes

Our primary outcome will be self-reported diagnostic confidence as measured by response to the survey question in the postvisit questionnaire that asks participants after reviewing the collective intelligence output for cases randomized to the intervention group: "How confident do you feel about your diagnosis for this patient?" (Not at all, somewhat, moderately, and very). We chose this outcome based on previous literature in diagnostic safety suggesting that diagnostic confidence plays an important role in medical management, evolves over time in the process of making a diagnosis, and the ability to move diagnostic confidence may contribute to avoiding diagnostic error [18,19]. Furthermore, our preliminary studies for the proposed trial suggested that clinicians' confidence in their clinical assessment is an important factor in their cognitive process for decision making and future approach to similar cases. We also chose this measure because it is likely the most sensitive to the impact of the collective intelligence on clinicians' complex diagnostic decision-making process, whereas clinical outcomes such as *time to diagnosis* and diagnostic accuracy can be confounded by external health care system factors such as time to receive test results, financial incentives for diagnostic testing, and other factors. The secondary outcome will be *time to diagnosis*, defined as the interval between the time of the clinic visit from which a case with diagnostic uncertainty was identified for entry into the collective intelligence platform and the time at which the clinician will have established a diagnosis for that symptom or sign. We will ascertain the time of established diagnosis as the time at which the clinician documents the new diagnosis, the result for a confirmatory diagnostic testing becomes available, or empiric treatment was initiated. We will choose the earliest occurrence of any of these three events as the time of established diagnosis.

Exploratory Clinical Outcomes

We will measure and analyze specified, additional outcomes that are relevant to the diagnostic process. We will define diagnostic accuracy as having the correct diagnosis listed in the top 3 answers of the collective intelligence output (for intervention cases) or in the top 3 of the clinician's list of possible diagnoses collected via survey data (for control cases). In addition, we will measure the number of diagnostic tests related to the initial complaint, ordered by the clinician within 30 and 90 days of the case presentation, and the number of unexpected visits (drop-in, urgent care, or emergency room) related to the initial presentation within 14 and 30 days of the index visit. Unexpected visits have been associated with higher risk of diagnostic error [1]. We refer to these as exploratory outcomes because we expect them to be highly variable both within and between clinicians and do not know whether we will have the statistical power to analyze them. Descriptive analyses of these outcomes may generate hypotheses for future study.

Satisfaction and Usability

We will use the exit survey and interview described above to assess the usability of collective intelligence to assist clinicians' diagnostic process in routine primary care and urgent care cases and examine their willingness to use collective intelligence in practice. Through the survey, we will determine the Net Promoter Score (NPS) as a quantitative measure of user satisfaction and willingness to use and a modified TAM score (overall and for each theoretical variable) as a quantitative measure of usability. The NPS is based on a single question: "How likely is it that you would recommend our service to a friend or colleague?" This score is increasingly used in health services research as a summary of consumer satisfaction [20]. The theoretical variables comprising the TAM score include PU, PEU, Trust, perceived facilitators, and intention to use.

Electronic Health Record Chart Review for Ascertainment and Adjudication of Outcomes and Other Variables

A total of 2 study investigators will independently review the medical record 6 months after the initial presentation of the case to ascertain the final diagnosis and exclude cases with persistent diagnostic uncertainty after 6 months. We will resolve discrepancies in adjudication by consensus. Our chart review will also capture the number of comorbid conditions (based on the problem list and the 10th revision of the International Statistical Classification of Diseases billing codes entered by the clinician for the visit), the type of visit (new, returning, drop-in, or urgent care), the number of diagnostic tests related to the initial presentation ordered by the clinician within 30 and 90 days of the case presentation, and the number of unexpected visits related to the initial presentation (drop-in, urgent care, or emergency room) within 14 and 30 days of the index visit. We will use the same 2-investigator adjudication process to ascertain diagnostic tests and unexpected visits related to the initial presentation.

Analysis Plan

Primary Outcome

We will perform a bivariate logistic regression with the intervention status (clinician access to collective intelligence output vs no access to collective intelligence) as the predictor and diagnostic confidence as the outcome, clustering on clinician. Self-reported diagnostic confidence will be treated as a categorical variable with "not at all" as the reference group.

Secondary Outcome

We will use Cox regression to compare time-to-diagnosis (T2Dx) between the intervention versus the control cases (ie, intervention status as primary predictor and T2Dx as outcome).

Survey Analysis

We will use *t*- test statistics to describe the NPS and TAM score (overall and for each variable) by clinician characteristic (NP vs MD; years of practice; and specialty—internal vs family medicine).

Exploratory Analyses

We will perform mixed-effect multivariable logistic regressions to compare diagnostic confidence, T2Dx, and diagnostic accuracy of intervention versus control cases, accounting for clustering by clinician and adjusted for baseline diagnostic uncertainty, perceived case difficulty, patient age, race, gender, number of comorbid conditions, type of visit (new, returning, drop-in, or urgent care), and primary care clinician characteristics such as professional degree (NP vs MD), specialty (family vs internal medicine), and years of experience. We have chosen covariates a-priori based on clinical judgment. For cases randomized to the intervention, mixed-effect bivariate logistic regressions will compare physicians' diagnostic accuracy before and after reviewing the collective intelligence, adjusted for the aforementioned clinician characteristics. We will use bivariate and multivariable linear regressions to compare the number of diagnostic testing and use logistic regressions to compare the occurrence of unexpected clinical visits at 30 days between intervention versus control cases.

Multiple Hypothesis Testing

We will report the results of the hypothesis test for the primary outcome without adjustment for multiple hypothesis testing. No formal penalization for multiple hypothesis testing is planned for the secondary, subgroup, or exploratory outcome analyses, as we will treat them as exploratory and hypothesis generating. We will report 95% CIs for all point estimates.

Handling of Missing Data

Our general approach to missing data will be multiple imputation. It is possible that our primary outcome of diagnostic confidence will have a level of missing data, as it will depend on the response rate to survey questions. In addition to multiple imputation under the standard assumption that data are missing at random, given the covariates and outcomes that are observed, we will also implement sensitivity analyses using imputation under plausible missing-not-at-random scenarios. To maximize survey completion rates and thereby minimize the level of missing data, we will send 3 email reminders at 3 days, 7 days, and 14 days if the initial survey request was not completed. We will leave hard copies of the survey in clinicians' mailboxes if the participants have not completed the online survey after the 3 email reminders.

Sample Size Justification

We planned our sample size using the primary outcome of clinician confidence in diagnosis, rated on a case-by-case basis. We anticipated an ability to detect (with 80% power) a 20% difference in clinicians rating their confidence in the case diagnosis as somewhat or very high, when comparing cases with versus without collective intelligence feedback. Assuming clustering of confidence ratings within clinicians at r=.3, we estimated that we need 33 clinicians with about 20 cases in total (10 with collective intelligence and 10 without collective intelligence; n=660 total cases).

Qualitative Analysis of Exit Interview

Qualitative analysis of interview transcripts will further examine barriers to usability and acceptance (ie, willingness to use) of the platform by clinicians in primary care clinical settings. Transcripts will be coded using an integrated inductive-deductive qualitative data analysis approach [21]. In particular, we will use the constant comparison method, an inductive qualitative data analysis approach in which data are broken down, compared for similarities and differences, and grouped together under similar conceptual themes [22] to uncover a wide variety of themes from the data, while also employing predetermined conceptual codes drawn from a modified TAM [23] to structure a deductive analysis of the data. A total of 2 study authors (KR and MH) will independently code the transcripts to identify preliminary themes through initial readings of the transcripts. Iterative discussions among all the study investigators will refine thematic categories and lead to a final set of salient themes identified across all the interviewees.

Results

At the time of manuscript submission, the trial is actively enrolling participants, and the recruitment started on August 20, 2018. We have recruited 32 out of our recruitment goal of 33 participants at the San Francisco Health Network (SFHN) and UCSF Health primary care clinics. The majority of clinicians (25) work within the SFHN, and 7 are from UCSF Health primary care clinics. This study is funded until May 2020 and is approved by the UCSF Institutional Review Board (#17-23839) until January 2020. We have completed data collection as of June 2019 and will complete our proposed analysis by December 2019.

Discussion

Diagnostic error is increasingly recognized as a significant public health concern. Extrapolations based on combining data from small studies suggest that approximately 12 million Americans experience a diagnostic error or delay every year in the ambulatory care setting [1]. However, to date, no prospective observational study of diagnosis in ambulatory care exists despite expert calls to address this important knowledge gap. Our study holds promise to close important gaps in the field of preventing diagnostic error in ambulatory care.

The study aims to improve diagnostic confidence in real-world ambulatory care settings using a collective intelligence technology platform that aims to assist primary care and urgent care clinicians in their diagnostic reasoning and decision making. Our robust mixed quantitative and qualitative analyses will help identify best use cases and clinical workflows for routine use of collective intelligence in ambulatory care. This work can then inform larger-scale work to estimate the impact of collective intelligence on diagnostic accuracy, and, ultimately, prevention of harm to patients. Findings will inform best practices to integrate digital health technology interventions for reducing diagnostic errors in primary care and urgent care clinics. This understanding can help with the adoption and tailoring of this and other collective intelligence platforms throughout safety-net health systems nationally.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Postvisit questionnaire.

[PDF File (Adobe PDF File), 88KB - resprot_v8i8e13151_app1.pdf]

Multimedia Appendix 2

Exit survey.

[PDF File (Adobe PDF File), 47KB - resprot_v8i8e13151_app2.pdf]

Multimedia Appendix 3

Interview guide for exit interview.

[PDF File (Adobe PDF File), 68KB - resprot_v8i8e13151_app3.pdf]

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Abbreviations

IT: information technology
MD: medical doctor
NP: nurse practitioner
NPS: Net Promoter Score
PEU: perceived ease-of-use
PU: perceived usefulness
SFDPH: San Francisco Department of Public Health
SFHN: San Francisco Health Network
T2Dx: time-to-diagnosis
TAM: Technology Acceptance Model
UCSF: University of California San Francisco

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Protocol

eRegTime, Efficiency of Health Information Management Using an Electronic Registry for Maternal and Child Health: Protocol for a Time-Motion Study in a Cluster Randomized Trial

Marie Hella Lindberg[1*], MPhil; Mahima Venkateswaran[2,3*], MBBS, MSc; Khadija Abu Khader[4], MPH; Tamara Awwad[4], MPH; Buthaina Ghanem[4], PharmD, MPH; Taghreed Hijaz[5], MSc; Kjersti Mørkrid[2], MPhil, PhD; J Frederik Frøen[2,3], MD, PhD

[1]Faculty of Health Sciences, UiT – the Arctic University of Norway, Tromsø, Norway

[2]Global Health Cluster, Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway

[3]Centre for Intervention Science in Maternal and Child Health, University of Bergen, Bergen, Norway

[4]Palestinian National Institute of Public Health, World Health Organization, Al-Bireh, Occupied Palestinian Territory

[5]Ministry of Health, Ramallah, Occupied Palestinian Territory

[*]these authors contributed equally

Corresponding Author:
J Frederik Frøen, MD, PhD
Global Health Cluster
Division for Health Services
Norwegian Institute of Public Health
PO Box 222 Skøyen
Oslo, 0213
Norway
Phone: 47 92 49 34 35
Email: frederik.froen@fhi.no

Abstract

Background: Paper-based routine health information systems often require repetitive data entry. In the West Bank, the primary health care system for maternal and child health was entirely paper-based, with care providers spending considerable amounts of time maintaining multiple files and client registers. As part of the phased national implementation of an electronic health information system, some of the primary health care clinics are now using an electronic registry (eRegistry) for maternal and child health. The eRegistry consists of client-level data entered by care providers at the point-of-care and supports several digital health interventions that are triggered by the documented clinical data, including guideline-based clinical decision support and automated public health reports.

Objective: The aim of the eRegTime study is to investigate whether the use of the eRegistry leads to changes in time-efficiency in health information management by the care providers, compared with the paper-based systems.

Methods: This is a substudy in a cluster randomized controlled trial (the eRegQual study) and uses the time-motion observational study design. The primary outcome is the time spent on health information management for antenatal care, informed and defined by workflow mapping in the clinics. We performed sample size estimations to enable the detection of a 25% change in time-efficiency with a 90% power using an intracluster correlation coefficient of 0.1 and an alpha of .05. We observed care providers for full workdays in 24 randomly selected primary health care clinics—12 using the eRegistry and 12 still using paper. Linear mixed effects models will be used to compare the time spent on health information management per client per care provider.

Results: Although the objective of the eRegQual study is to assess the effectiveness of the eRegistry in improving quality of antenatal care, the results of the eRegTime study will contribute to process evaluation, supplementing the findings of the larger trial.

Conclusions: Electronic health tools are expected to reduce workload for the care providers and thus improve efficiency of clinical work. To achieve these benefits, the implementation of such systems requires both integration with existing workflows and the creation of new workflows. Studies assessing the time-efficiency of electronic health information systems can inform policy decisions for implementations in resource-limited low- and middle-income settings.

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KEYWORDS

health information systems, eHealth; Time and Motion Studies; workflow; antenatal care; developing countries

Introduction

Background

Robust health information systems play a central role in the strengthening of health systems and achieving universal health coverage [1-4]. There are, however, substantial gaps in the reliability, timeliness, and efficiency of health data collection, analysis, and use in many countries, hampering evidence-based decision making at all levels of the health system [5]. Common traits of many health systems include inefficient and uncoordinated data processing and management [6]. Health care providers are often obliged to repeatedly collect, compile, and report redundant health information. Therefore, time spent on direct patient care might be shortened [5,7]. The introduction of health information technologies could substantially influence care providers' workflow and clinical work processes [8,9]. Existing evidence, primarily from high-income contexts, suggests that access to relevant health information tends to improve with the use of electronic health information systems but is often associated with time-consuming and counterintuitive user-system interactions [10-14]. There is limited evidence from low- and middle-income countries (LMICs) on how the use of electronic health information systems affect clinical workflow or efficiency [15,16]. LMIC can least afford wasting the time of a limited health workforce and may gain the most from improved efficiency of health information management [17,18]. It is therefore important to detect and understand the specific challenges faced in settings with fewer resources to successfully and sustainably implement electronic health information systems in such contexts.

In the West Bank, Palestine, an electronic health information system—the eRegistry for maternal and child health—is currently being rolled out on a national scale throughout primary health care. The eRegistry consists of electronic health (eHealth) records for antenatal, postpartum, and newborn care for use at the point of care by the care providers. The eRegistry supports automated clinical decision support, workflow management support, and referral functionalities. [1,19-21]. Care providers in primary health care clinics can access the eRegistry through desktop computers where they enter all client-related information [22]. The Palestinian eRegistry is installed in the District Health Information System 2 (DHIS2) tracker software; DHIS2 is a Web-based platform that is free and open-source and currently in use in more than 50 low- and middle-income settings largely for collection of aggregate data in a health information system or, to a lesser extent, for individual-level data in the health system.

An ongoing cluster randomized controlled trial (CRCT), the eRegQual study, is embedded in the national implementation of the eRegistry, where clinics using the eRegistry were included in the intervention arm and compared with the control arm that used paper-based records [22]. The primary objective of the eRegQual CRCT is to assess the effectiveness of the eRegistry in improving health outcomes for pregnant women and process outcomes of quality of antenatal care. Further details of the eRegQual study can be found in the published trial protocol [22].

The time-motion method is one of the more robust study designs for the collection and quantification of time data [8] and has been used to study costs and inefficiencies in the delivery of health care as well as patient safety and quality [23]. The time-motion study design in health care involves continuous observations of clinicians' work in health facilities by recording the time taken to perform a set of predefined tasks. This study design is frequently applied in assessing whether the introduction of an eHealth tool is associated with changes in time-efficiency [24].

Objectives

The aim of the eRegTime study is to evaluate whether the use of an eRegistry changes the time-efficiency of care providers in primary health care clinics for antenatal care. Time-efficiency will be assessed by measuring the time spent by the care providers on health information management.

Methods

In this protocol, we have followed the Suggested Time and Motion Procedures checklist for standardized reporting of studies using the time-motion design (see Multimedia Appendix 1) [8] as well as the Standard Protocol Items: Recommendations for Intervention Trials checklist (see Multimedia Appendix 2).

Setting

In the West Bank, Palestine, primary health care clinics provide antenatal, postpartum, and newborn care.

The different cadres of health care providers that work in maternal and child health in primary health care clinics include midwives, nurses, general practitioners trained in maternal and child health care, and specialist obstetricians. Smaller clinics (less than 50 new enrollments of pregnancies a year) typically have a nurse or a midwife working throughout the week, whereas the doctor visits the clinic once every 2 weeks. Larger clinics (more than 50 new enrollments of pregnancies a year) and referral clinics have specialist obstetricians, in addition. The nurse or midwife in the clinics does the majority of the antenatal care consultation and after-consultation work that involves health information management and were the only groups of care providers observed in this study.

The phased national implementation of the eRegistry was undertaken in tandem with the eRegQual study; the intervention clusters of the eRegQual study were the clinics that received

the eRegistry as part of phase 1 of implementation, whereas control clusters continued to use paper-based clinical records and were scheduled to receive the eRegistry after the end of the eRegQual study. Although 68 primary health care clinics started using the eRegistry in phase 1 of implementation, and 59 clinics continued to use paper-based clinical records, some of the smaller clinics were clubbed to form clusters before randomization for the eRegQual study. Larger clinics were considered as clusters of their own. In total, there were 60 clusters in each arm of the eRegQual study. Details of enrollment and randomization for the eRegQual study can be found in the published trial protocol [22].

The intervention evaluated in the eRegQual study—the eRegistry—is used as a point-of-care electronic data entry tool in primary health care clinics in the West Bank [22]. Guideline-based clinical decision support and automated electronic monthly reports are 2 digital health interventions currently supported by the Palestinian eRegistry. The eRegistry is intended to fully replace paper-based systems for maternal and child health in primary health care in the West Bank.

Workflow in Primary Health Care Clinics

Workflow in Clinics Using Paper-Based Systems

Pregnant women visit primary health care clinics for their first antenatal (booking) visit on specific workdays (clinics may work 1-4 days a week). The nurse or midwife in the clinics receives the pregnant women for the booking visit and documents a set of demographic data (eg, name, national identification number, address, phone number, and date of birth), and medical, surgical, and obstetric history. Afterward, the nurse or midwife measures and documents the woman's height and weight, blood pressure, and fundal height and orders and fills out routine laboratory results appropriate for each antenatal visit. As part of the booking visit, the doctor examines women on the same workday or a few workdays later in some clinics. The nurse or midwife assists the doctor in medical and ultrasound examinations. For pregnant women identified with risk factors that warrant a referral, the nurse or midwife makes necessary arrangements for transfer to the referral health facility. There is a flexible appointment system for all subsequent antenatal visits. For uncomplicated pregnancies, the nurse or midwife documents blood pressure and fundal height, checks for fetal presentation, and orders laboratory investigations during the subsequent antenatal visits. Nurses and midwives typically do client care for pregnant and postpartum women as well as newborns in the first part of the workday. Following this, the nurse or midwife usually completes registers for antenatal care, referrals, ultrasounds, vaccines, and laboratory investigations. The nurse or midwife also compiles the data in the registers for public health reporting to the Palestinian Ministry of Health, typically concentrating this task in 1 or 2 workdays monthly. Event counts of number of pregnancies registered in the clinic, number of ultrasound examinations and laboratory tests that are performed, and number of pregnancies with risk conditions that are referred are some examples of the data that are part of standardized monthly reports submitted by care providers [25].

Workflow in Clinics Using the Electronic Registry

All clinical tasks, as described for the control clusters, are identical in case of the intervention clusters. Only the health information management differs. The eRegistry is used by care providers to document real-time clinical data during client consultation. On the basis of the data entered at the point of care, the eRegistry generates automated decision support and workflow assistance [19,22]. Laboratory systems are not integrated in the eRegistry, and care providers need to enter the laboratory results they receive on paper into the eRegistry retrospectively. The eRegistry aggregates and submits all data that are part of the public health reports automatically every month to the Palestinian Ministry of Health.

Study Design

The time-motion study design was employed to collect data in the eRegTime study [8,24]. Observations were conducted in a randomly selected subsample of intervention and control clusters (primary health care clinics) of the eRegQual CRCT.

Outcome Measures

The primary outcome measure is the time spent on health information management per consultation. We defined health information management as the preparations and executions of collection, aggregation, analysis, and dissemination of clinical data, both at the individual and aggregate levels [26]. To tailor the general definition of the primary outcome to fit our context, we first used workflow mapping exercises ahead of data collections for the eRegTime study (as described previously) to list all the tasks usually done by the nurse or midwife in the primary health care clinics during antenatal care on a typical workday [27]. We then defined 6 activity types corresponding to the tasks: accessing information, reporting, documentation, client care, client-related care, and miscellaneous. The primary outcome measure—health information management time—was defined as time spent on all tasks involving the activity types "information access," "information documentation," and "information reporting" (see Table 1) [27]. "Information access" includes all activities that involve seeking and finding relevant existing health or demographic information on the client [27]. "Information documentation" consists of all tasks that involve writing down client information in the antenatal records (electronic or paper), laboratory, and ultrasound forms [27]. "Information reporting" is defined as transferring information from the antenatal records and registers for public health reporting [27].

A total of 2 additional analysis categories were defined: (1) "client care" that includes all activities in which the care provider is fully focused on the client without any writing and (2) "client-related care" that refers to all tasks that are imperative for care of individual pregnant women undertaken between 2 antenatal care consultations (see Table 1).

Activities unrelated to care of clients, including personal activities of the care providers, and tidying and preparing the consultation room for new clients, were categorized as "miscellaneous" (see Table 1) [27].

Table 1. Analysis categories including the primary outcome measure, corresponding task, and task category as defined for data collection (adapted from the study by Pizziferri et al [30] and tailored to the local context).

Analysis category	Task category in data collection tool	Name of task in data collection tool
Client care	Outside	Assisting doctor
Client care	Outside	Examination in other room
Client care	Procedures	Clinical and medical examination
Client care	Procedures	Injections and bloodtake
Client care	Procedures	Giving tablets
Client care	Procedures	Other
Client care	Talking	Education and counseling
Client care	Talking	Talking to family
Client care	Talking	History: demographic and medical
Client care or client-related care[a]	Talking	Clinical support
Client care or client-related care[a]	Talking	Call client or family
Client care or client-related care[a]	Talking	Referrals
Client care or client-related care[a]	Talking	Other
Health information management	Between or after consultations	Writing in statistics book
Health information management	Computer-Find	Client file
Health information management	Computer-Find	Lab or ultrasound results
Health information management	Computer-Writing	Client file (including history)
Health information management	Computer-Writing	Lab or ultrasound form
Health information management	Computer-Writing	Schedule appointment
Health information management	Computer-Writing	Text message in eRegistry
Health information management	Paper-Find	Client file
Health information management	Paper-Find	Lab or ultrasound results
Health information management	Paper-Writing	MCH (Maternal and Child Health) Handbook (including history)
Health information management	Paper-Writing	Client file (including history)
Health information management	Paper-Writing	Register book
Health information management	Paper-Writing	MCH Handbook or register book
Health information management	Paper-Writing	Register book or client file
Health information management	Paper-Writing	Client file or MCH handbook
Health information management	Paper-Writing	Lab, ultrasound, prescriptions, and referrals
Health information management	Paper-Writing	Schedule appointment
Health information management	Paper-Writing	Writing on other paper
Health information management	Talking	Explaining test results
Health information management	Talking	Technical support
Health information management or client-related care[b]	Computer-Read	Appointment list
Health information management or client-related care[b]	Computer-Read	Client file
Health information management or client-related care[b]	Computer-Read	Lab or ultrasound results
Health information management or client-related care[b]	Computer-Read	Guidelines, treatment
Health information management or client-related care[b]	Computer-Read	Other info
Health information management or client-related care[b]	Paper-Read	Appointment list

Analysis category	Task category in data collection tool	Name of task in data collection tool
Health information management or client-related care[b]	Paper-Read	MCH handbook
Health information management or client-related care[b]	Paper-Read	Client file
Health information management or client-related care[b]	Paper-Read	Lab or ultrasound results
Health information management or client-related care[b]	Paper-Read	Treatment guidelines
Health information management or client-related care[b]	Paper-Read	Other info
Miscellaneous	Between or after consultations	Cleaning, arranging files
Miscellaneous	Between or after consultations	Phone and computer (personal)
Miscellaneous	Between or after consultations	Other: praying, eating, toilet
Miscellaneous	Between or after consultations	Eating, praying, toilet
Miscellaneous	Between or after consultations	Group education
Miscellaneous	Postpartum care	Postpartum care

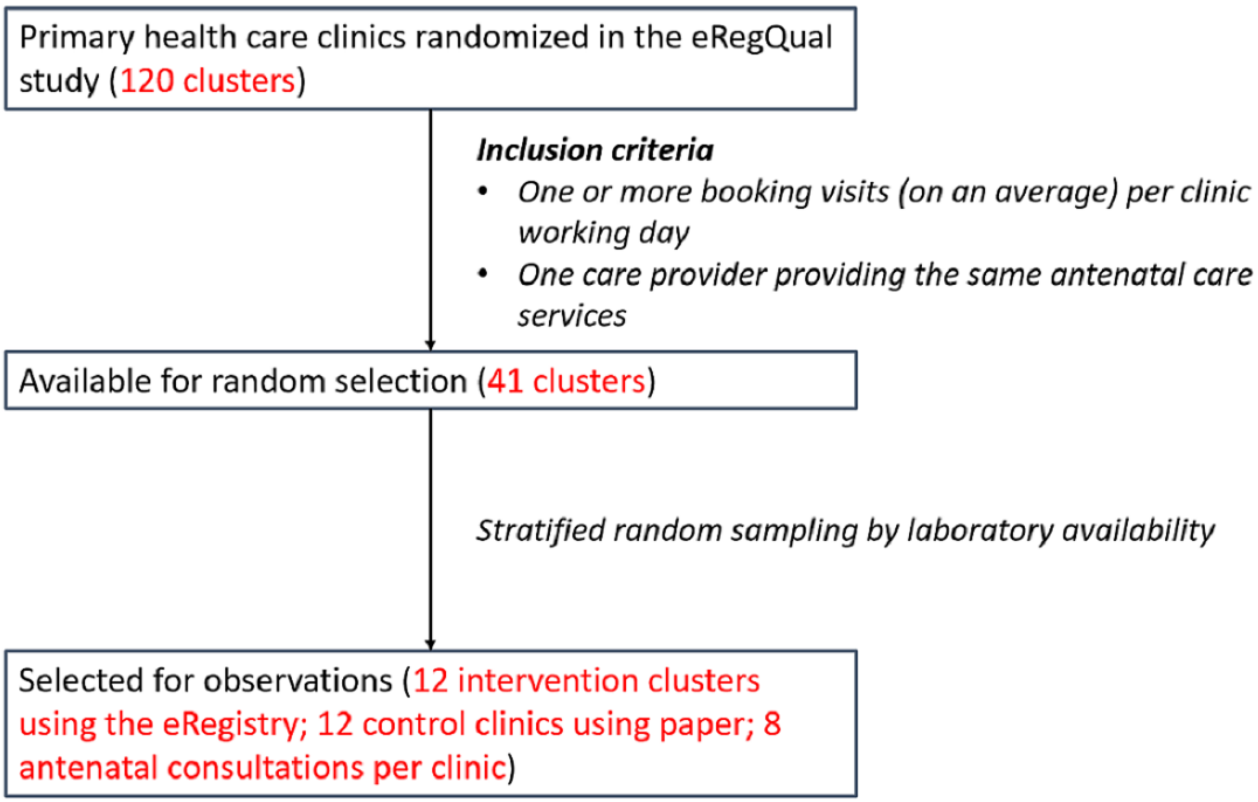
[a]Task classified as client-related care if done outside of a consultation. If done within an antenatal care consultation, it is classified as client care.

[b]Task classified as client-related care if done outside of a consultation. If done within an antenatal care consultation, it is classified as health information management.

Eligibility Criteria

Clusters (primary health care clinics) that are part of the eRegQual CRCT that fulfil the following criteria were eligible for inclusion in the eRegTime study: (1) Have 1 nurse or 1 midwife providing antenatal care services on a given workday (to maintain a 1:1 subject-to-observer ratio) and (2) Have, on average, at least 1 booking visit per workday (to ensure capturing a sufficient number of antenatal booking visits). After applying these inclusion criteria to the 120 clusters that are part of the eRegQual CRCT, 41 clusters were eligible for the time-motion study observations (20 intervention clusters and 21 control clusters; Figure 1).

Figure 1. Selection of clusters in primary health care clinics for observations.



Sampling

For sample size estimations, we assumed that clinics using paper-based systems spend an average of 10 min on health information management per client. We also assumed unequal and higher SD around the mean health information management time (in minutes) for clinics that use the eRegistry (SD=5) compared with clinics that use paper-based systems (SD=2) because of an expected variance in computer literacy and confidence of use. Sample size calculations were made using the Stata command "clustersampsi" to detect a 25% difference at a 90% power and 5% significance using an a priori intracluster correlation coefficient of .1 [28,29]. A total of 24 primary health care clinics were selected to be observed, 12 from each arm of the CRCT, with at least 8 observed antenatal consultations per clinic (Figure 1). Statisticians that are independent of the eRegTime study team performed a random sampling of the primary health care clinics for the observations, stratified on laboratory availability.

Data Collection Methods

We designed the data collection tool based on a Microsoft Access database template made available online by the US Agency for Healthcare Research and Quality [24], customized to the clinical workflow in the West Bank. The data collection tool was installed on handheld tablets. The data collection tool contains a list of tasks categorized under 10 task categories, and every task can be time-stamped (Figure 2) [30,31]. The task categories covered the care providers' entire workday consisting of every clinical and nonclinical task, including after-consultation and between-consultation work.

The observers were trained to first determine the nature of the observed task and then click on the corresponding task on the data collection tool (Figure 2) [32]. The observer could end a task by clicking on the "confirm entry" button (Figure 2). In case of multitasking by the care providers, the observers were instructed to select the principal activity. After-consultation work were recorded as separate observations, as were postpartum care consultations.

The database stored the observation times for each task with an activity code linked to the tasks. In accordance with ethical approvals for the study, no personal or other demographic data related to the client or the care provider were collected, and clinic names were only being stored as computer-generated codes in the database.

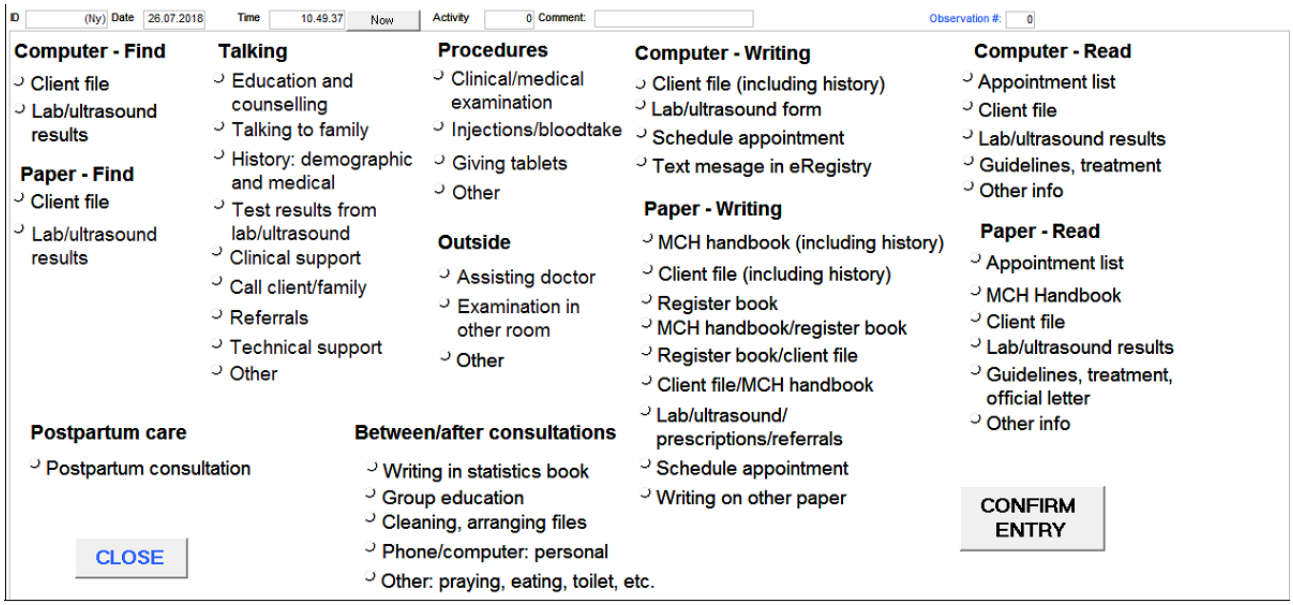
A total of 4 trained observers completed the data collection. Observers were trained with simulation videos on the time-motion methodology and the task categories and in using the data collection tool (see Multimedia Appendix 3). Following training, the observers conducted practice observations in nonstudy clinics with and without the eRegistry. After this, observations and data collections were undertaken in the study clinics. The observers recorded a full workday and included all the antenatal consultations during that day. If the required number of antenatal consultations per clinic (n=8) was not achieved in 1 day, additional days of observation were carried out until the required cluster size was reached.

The field coordinators of the study received the data after each day of data collection and checked that the sample size for each clinic is reached with a sufficient number of documented observations.

Blinding

Although neither the observers nor the care providers in the primary health care clinics can be blinded to the intervention, they both will be blinded to the outcomes of the eRegTime study and have only been informed of the overarching objective of the eRegQual CRCT (including the eRegTime study) of assessing effects of the eRegistry on the quality of care. To ensure blinding of the observers to the outcome, the data collection tool included an exhaustive list of tasks, beyond the primary outcome of the eRegTime study (see Table 1; Figure 2).

Figure 2. Data collection tool (data entry form) used for recording time-motion data.



Data Analyses

The unit of measurement of the primary outcome is the time spent on health information management per client per care provider, where time will be analyzed in minutes. Statistical analyses will be performed using Stata version 15 or later (StataCorp LLC, 2017, *Stata Statistical Software: Release 15*) or RStudio version 1.2.1335 or later. Descriptive statistics for the time variables will be summarized as means and SDs. We will report on the average time spent on antenatal consultation overall, and for booking visits and other antenatal visits separately, and the average time spent on each of the activity types including those that are not part of the primary outcome (including "client care," "client-related care," and "miscellaneous"; see Table 1).

We assume that the nurse or midwife spends, on average, an equal amount of time on after-consultation documentation work per client. The after-consultation time spent on client-related documentation and public health reporting will be averaged over the number of observed antenatal consultations and added to the time spent per consultation. Differences in the health information management time between the clinics with and without the eRegistry will be tested for significance using the linear mixed effects model to account for clustering [33,34]. In addition, as secondary analyses, we will test for differences in the health information management time separately for booking visits and other antenatal visits, and differences in time spent on other activity types in the 2 arms. Postpartum care consultations will be excluded from the analysis, as the focus of both eRegQual and eRegTime studies is on antenatal care quality and clinical processes.

Accompanying the results of the outcomes of the study, interobserver reliability assessments will be reported using kappa coefficients for the total number of clinical tasks and activity types recorded and intraclass correlation coefficients for the recorded mean times for the tasks and analysis categories (see Table 1) [35].

Ethics Approval and Consent to Participate

The eRegTime study was approved by the Palestinian Health Research Council (PHRC/HC/208/17) and the Regional Committee for Medical and Health Research Ethics in Norway (2017/400). Permissions to conduct observations in the clinics have been obtained from the Palestinian Ministry of Health. Care providers and supervisors of the primary health care clinics will be informed of the data collection for this study. Considering the local sensitivity and hesitance related to signing documents in our study context, pregnant women will be asked for oral consent to allow the observers to be present in the rooms during consultations, and the ethics committees were notified of this. No data will be recorded on personal or individual characteristics of pregnant women, care providers, or primary health care clinics. Only completely anonymous data will be available to the researchers for analysis.

Results

Ethical approvals for conduct of the study were obtained in April 2017. The data collection tool was designed, tested, and adjusted over 2017 and 2018, followed by which the sample was selected for the main study. Clinics included in the sample were informed about the study before start of observations, and the data collection for the eRegTime study was completed between August and December 2018. Data will be analyzed for outcomes in July and August 2019; the results are expected to be published in the second half of 2019.

Discussion

The eRegTime study is one of the few studies that assesses the impact of an eHealth intervention on clinical workflow and time-efficiency in a middle-income context, where the impact of using digital tools routinely during clinical care is probably much bigger given the manpower and resource constraints than high-income settings.

Most studies that have assessed the time-efficiency using the time-motion design find no statistical differences in the workload of care providers following the introduction of eHealth tools [15,30,31,36]. Factors that may potentially affect the time-efficiency of care providers while using eHealth tools are duration of use of eHealth tools, computer literacy, multitasking, and interruptions [37-41]. In some settings, a period of 18 to 24 months between the implementation of the eHealth tools and the observations was considered sufficient for the stabilization of clinical work routines [15,42]. Primary health care clinics observed in the eRegTime study will be using the eRegistry for a median time of 20 months at the time of the observations. According to a questionnaire survey conducted in the intervention clusters of the eRegQual CRCT, a quarter of the nurses and the midwives had never used a computer before starting to use the eRegistry. Formative research and workflow mapping exercises showed that health care service delivery in the setting of this study was characterized by fragmented workflow and the time taken to perform the different tasks was relatively short [27]. The time-motion design is particularly suitable for data collection in such settings [30,31]. Although interruptions to the workflow and multitasking might be overlooked because of the fact that the data collection tool requires the observer to select only 1 activity at the time, the primary objective of the eRegQual study is to assess quantitative differences in time spent between clinics with and without the eRegistry; data collection methods were designed to be identical in the 2 arms.

Other methods such as work sampling and self-reported questionnaires were considered during the planning phase of this study. However, with work sampling, in which activities are recorded only at certain time intervals, there is a risk of missing certain activities. In addition, this method requires an enormously large sample size, which was not feasible in our setting [43]. The use of self-reported questionnaires poses risks of inaccurate reporting and recall bias as well as being a considerable interference to the care provider's workflow [44]. The time-motion design was therefore considered the most suitable for this study.

We acknowledge that it may not be possible to completely eliminate the risk of care providers behaving differently because they know they are being observed [45]. We will attempt to

minimize this effect by training the observers to avoid interfering with clinical work [45]. Another potential source of bias is diverging subjective interpretations of the tasks during data collection by the observers, and this will be minimized by hands-on training sessions, practice sessions with simulation videos, and "test" observations before the start of the study observations.

Acknowledgments

The first author MHL, with supervision from Knut Reidar Wangen, conducted formative research for this study as part of a master thesis at the University of Oslo, sections of which also informed this protocol. The eRegTime study is conducted in cooperation with the Ministry of Health, Palestine and the Palestinian National Institute of Public Health, who will facilitate the training of the observers and the implementation of the study.

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Authors' Contributions

MHL designed the data collection tool, conducted formative research including mapping clinical workflows, and defining task categories. MHL and MV contributed to the study design, sample size estimations, and formulation of outcomes and the writing of this study. KM contributed to the study design and formulation of the outcomes and the formative research. BG, TA, KAK, and TH participated in the design of the data collection tool. TA, KAK, and TH conducted pilot observations in the clinics. JFF is the principal investigator of the eRegQual CRCT and contributed to the study design, objectives, outcomes, and the writing of this study. All authors have read and approved of this version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Suggested Time and Motion Procedures (STAMP) checklist.

[PDF File (Adobe PDF File), 585KB - resprot_v8i8e13653_app1.pdf]

Multimedia Appendix 2

SPIRIT protocol checklist.

[PDF File (Adobe PDF File), 235KB - resprot_v8i8e13653_app2.pdf]

Multimedia Appendix 3

Training manual.

[PDF File (Adobe PDF File), 719KB - resprot_v8i8e13653_app3.pdf]

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Abbreviations

CRCT: cluster randomized controlled trial
DHIS2: District Health Information System 2
eHealth: electronic health
eRegistry: electronic registry
LMIC: low- and middle-income country

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Protocol

Mental Health Promotion Among University Students Using Text Messaging: Protocol for a Randomized Controlled Trial of a Mobile Phone–Based Intervention

Kristin Thomas[1], PhD; Marcus Bendtsen[1], PhD

Department of Medical and Health Sciences, Faculty of Medicine, Linköping University, Linköping, Sweden

Corresponding Author:
Kristin Thomas, PhD
Department of Medical and Health Sciences
Faculty of Medicine
Linköping University
Linköping, 58183
Sweden
Phone: 46 13282546
Email: kristin.thomas@liu.se

Abstract

Background: There is a growing understanding that well-being and mental illness are 2 separate dimensions of mental health. High well-being is associated with decreased risk of disease and mental illness and increased longevity.

Objective: This study aims to test the efficacy of a mobile phone–based intervention on positive mental health.

Methods: We are conducting a 2-armed randomized controlled trial of university students in Sweden. Recruitment will last for 6 months by digital advertising (eg, university websites). Participants will be randomly allocated to either an intervention (fully automated mobile phone–based mental health intervention) or control group (treatment as usual). The primary outcome will be self-assessed positive mental health (Mental Health Continuum Short Form). Secondary outcomes will be self-assessed depression anxiety symptomatology (Hospital Anxiety Depression Scale). Outcomes will be investigated at baseline, at 3, 6, and 12 months after randomization. Mediators (positive emotions and thoughts) will be investigated at baseline, midintervention, and at follow-ups using 2 single face-valid items.

Results: Data will be collected between autumn 2018 and spring 2019. Results are expected to be published in 2020.

Conclusions: Strengths of the study include the use of a validated comprehensive instrument to measure positive mental health. Mechanisms of change are also investigated. A potential challenge could be recruitment; however, by setting a prolonged recruitment period, we believe that the study will recruit a sufficient sample.

Trial Registration: International Standard Randomized Controlled Trial Number: 54748632; http://www.isrctn.com/ISRCTN54748632

International Registered Report Identifier (IRRID): PRR1-10.2196/12396

(JMIR Res Protoc 2019;8(8):e12396) doi:10.2196/12396

KEYWORDS

mental health; telemedicine; students; randomized controlled trial

Introduction

Background

Mental well-being has traditionally been perceived as simply the absence of mental illness [1]. There is now evidence that positive mental health and mental illness are 2, albeit connected, unique dimensions of mental health. Positive experiences such as personal growth or feelings of hope can occur alongside mental illness. Similarly, the absence of mental illness does not mean automatic presence of positive mental health. Indeed, people afflicted by mental illness can have experiences of personal growth and feelings of hope, indicating that well-being and mental illness are not mutually exclusive [1-5].

Strong positive mental health is associated with various benefits including decreased risk of disease [6-10], decreased risk of mental illness [11-14], and increased longevity [8,15]. In a

cohort study, individuals with poor positive mental health were 7 times more likely to be depressed 10 years later [14]. Individuals with poor positive mental health score similar to, or worse than, clinically depressed individuals on outcomes such as everyday functioning (eg, number of days absent from work) and psychosocial functioning (eg, achieving goals) [16]. The promotion of positive mental health among the general population has, therefore, recently been emphasized as the most important goal for the public mental health agenda in Europe [17].

Positive psychology interventions (PPIs) aim to promote positive mental health [18,19]. For example, a brief exercise where the individual is asked "to think about three things that went well during the day and savor those moments" have shown to increase positive mental health [9,19]. The positivity-activity model proposes that PPIs affect the relationship between positive practice (eg, acts of kindness) and well-being through increased positive emotions, thoughts, and behaviors. Furthermore, that features of positive practices (eg, how often do you perform acts of kindness) and individual factors (eg, motivation to be kind) moderate the relationship between positive practice and well-being [20].

Meta-analyses show that PPIs have a small effect on positive mental health in healthy volunteers and clinical populations [9,19]. However, 1 meta-analysis including 39 randomized controlled trials on the effect of PPIs showed that the quality of studies varied significantly, for example, blinding of participants, indicating a need for more rigorous studies. In addition, the majority of studies have investigated the effect of individual exercises targeting 1 aspect of positive mental health per se limiting the external validity of the results (eg, using a gratitude journal to increase positive thinking).

There is high acceptance among the general population to use mobile technology for health self-management, [21] and technical interventions can offer privacy and an emotionally safe environment [22]. Interventions using short message service (SMS) text messages are feasible to implement on a population level as nearly all people have a mobile phone; interventions could, therefore, reach a large proportion of a target group at low costs [23,24]. Thus, mobile phone–based interventions could be a cost-effective choice for mental health promotion and disseminating PPIs to larger audiences.

There is a great number of mobile apps commercially available aiming to promote mental health among the general population. A review of hundreds of these apps discovered that the majority lacked experimental evidence, were not theory-based, and had not been scientifically evaluated [25]. The research literature shows promising results whereby mobile phone–based interventions can increase well-being. A review on the effect of digital interventions (eg, mobile apps) on mental health showed a small to medium effect where mental health problems decreased and positive mental health increased. However, the overall quality of the studies was relatively low regarding risk of bias [26]. Another review summarized the evidence for theory-driven and evidence-based mental health electronic resources (e-resources; eg, website or mobile apps) and only found 1 randomized controlled trial. The authors concluded that e-resources for mental health have the potential to be widely effective; however, more rigorous studies that can clarify the evidence base are needed [27].

In addition, there is limited understanding on *how* PPIs work, that is, what mechanisms contribute to an increase in positive mental health? Although evidence suggests that PPIs elicit positive thoughts, emotions, and behaviors, which in turn increase well-being, few studies have investigated this proposition in the context of mobile phone interventions [20,28].

Objectives

This protocol describes a randomized controlled trial that aims to test the efficacy of a fully automated mobile phone–based intervention on positive mental health among university students. The primary hypothesis is that participants in the intervention group will report significantly higher positive mental health (measured by the primary outcome measure) at follow-up compared with participants in the control group. Secondary hypotheses are that the intervention group will report significantly higher emotional, social, and psychological well-being as well as significantly lower rates of anxiety and depression symptomatology (measured by primary and secondary outcomes) at follow-ups compared with participants in the control group. These hypotheses are proposed at 3-, 6-, and 12-month follow-ups. Positive emotions and thoughts are hypothesized to mediate the relationship between access to the intervention and outcomes.

Methods

Design

A 2-arm randomized controlled trial will be conducted where participants will be equally allocated to either an intervention (mobile phone–based program) or control group (treatment as usual). No strata or blocks will be employed, and the randomization procedure will not be subverted as this and all subsequent study processes are fully automated.

Outcomes and Measures

A baseline questionnaire will investigate demographic data (age, gender, and social status), primary outcome [2], and secondary outcomes [29]. Follow-up questionnaires will investigate primary and secondary outcomes. Outcomes will be investigated at baseline and at 3, 6, and 12 months after randomization. Participants will receive and complete questionnaires through their mobile phones.

Primary outcome will be positive mental health, assessed with the 14-item Mental Health Continuum Short Form (MHC-SF) [2]. Higher scores indicate greater emotional, social, and psychological well-being (range 0-84). Secondary outcomes will be depression and anxiety symptomatology assessed as the score on corresponding subscales of the Hospital Anxiety Depression Scale (HADS) [29].

To investigate mediators of the intervention [20], 2 face-valid items will measure the frequency of positive thoughts (''During the last week, to what extent have you experienced positive thoughts" and "During the last week, to what extent have you experienced positive emotions"). Items will be rated on a scale

ranging from 0= *not at all* to 9= *to a very high extent*. Mediators are assessed at baseline, midintervention (end of week 5), and at subsequent follow-ups. Mediation scores are hypothesized to be significantly higher in the intervention group compared with the control group.

Participants and Inclusion and Exclusion Criteria

Inclusion criteria will be university students aged 18 to 29 years, able to read and understand Swedish, and owning a mobile phone. Exclusion criterion will be strong positive mental health defined as a score of 70 or more on the MHC-SF [2], as these individuals already demonstrate high positive mental health. A second exclusion criterion will be depression and anxiety symptomatology defined as a score of greater than or equal to 10 on both subscales of the HADS [29]. Owing to the proposed intervention not being a treatment program for HADS, these individuals will be given information about where to receive support.

Intervention Group

The intervention is a fully automated mobile phone–based positive psychology multicomponent program. The content is based on the positive-activity model [20] and empirical evidence of PPIs from the positive psychology research field. The program runs for 10 weeks with a new theme being introduced each week. Each theme has shown to contribute to positive mental health in previous research: gratitude, savoring, positive emotions, personal strengths, positive relations, social environment, health behaviors, optimism, and goal setting (eg, [30-33]). During the last week, the user is guided to plan for the future and reflect on the program, for example, lessons learnt.

The program aims to increase users' positive mental health and includes information about well-being, validated self-help exercises, tips, self-monitoring, and personalized feedback. The SMS text messages include text and links to pictures, interactive exercises, and further reading. SMS text messages are automatically sent to users throughout the program with on average 1 SMS text message a day.

Control Group

Individuals allocated to the control setting will be informed of this through an SMS text message. The SMS text message will also include contact details of their local student health service, primary care center, or governmental national health website (treatment as usual).

Sample Size

A power analysis was conducted to determine the necessary number of participants to invite to the study. To detect a standardized effect size of 0.3, so as to have the average score in the intervention group exceeding the scores of 62% of the control group, a total of 352 participants are required. The calculations were done assuming an 80% chance of detecting the difference at a significance level of .05 (2-tailed). Assuming that 70% of the participants respond to the follow-up questionnaire, it is necessary to recruit 503 participants in total. Furthermore, assuming that 1% of the invited population is willing to join the study (and are not excluded), we need to invite 50,300 participants.

Recruitment

Students from 11 universities in Sweden will be invited to take part. Recruitment will last for 6 months and be executed by digital advertising (email, university websites, Student Health Services websites, and learning management systems used by the universities). The universities are located throughout Sweden in rural and urban settings. Faculties from medical, technical, art, and social sciences will be represented. The advertisement will include information on the study aims, confidentiality, and trial design. Students will register their interest by sending an SMS text message to a dedicated telephone number (included in the advertisement material). Informed consent and the baseline questionnaire will be completed on their mobile phone. After completing the baseline questionnaire, students will then automatically be randomized to either an intervention or control group. Participants will know that they have been randomized to either an intervention or control group. Figure 1 depicts a flowchart of the recruitment procedure of the study.

Randomization

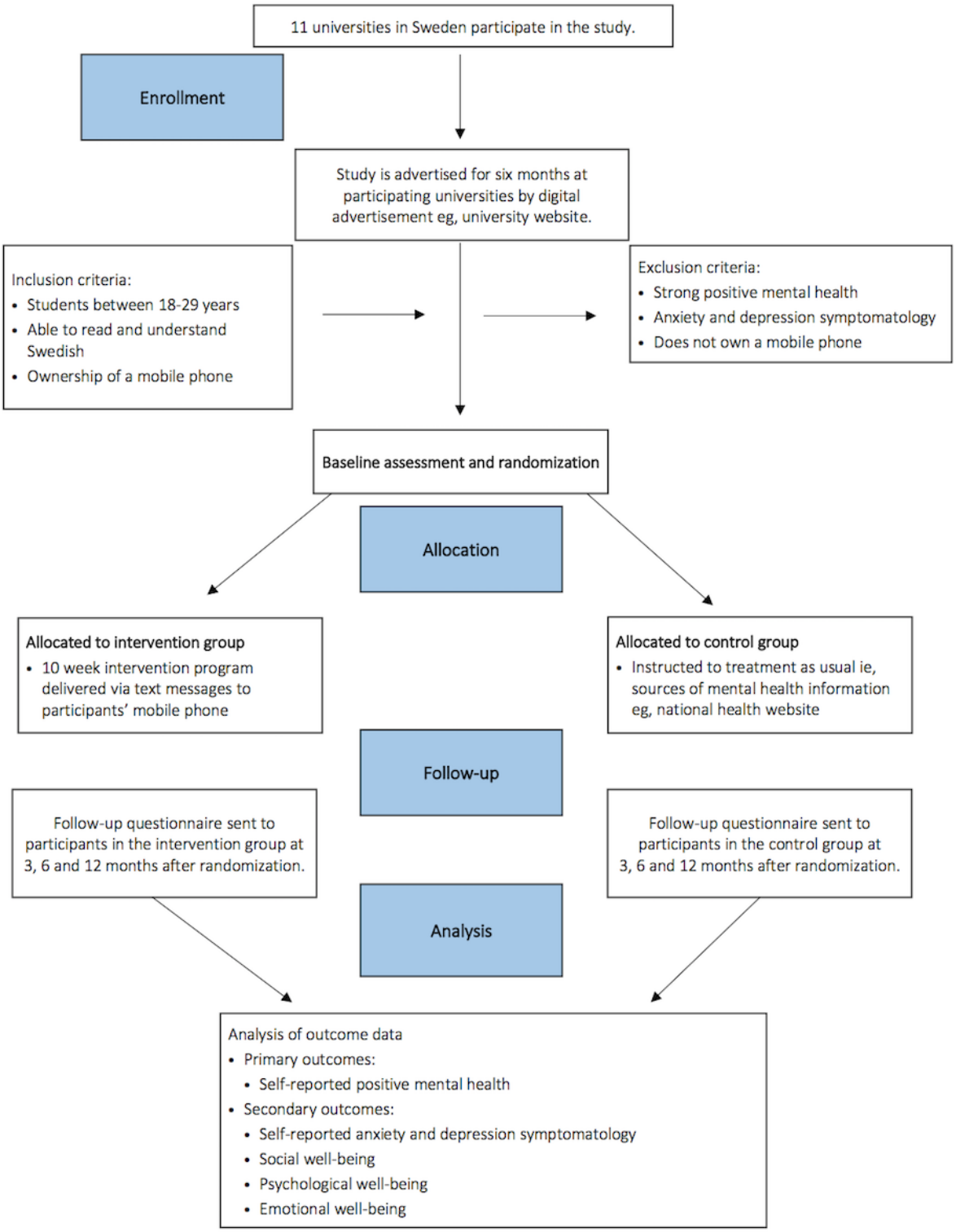
Participants will be randomized to either the intervention or control group. Each participant will be allocated a number 1 or 2 with equal probabilities using Java's built-in random number generator (java.util.Random). Randomization is thus fully computerized, does not use any strata or blocks, and is not possible to subvert because this and all subsequent study processes are fully automated.

Statistical Methods

All analyses will be done under the intention-to-treat principle, where all randomized individuals will be included. Missing outcome data will initially be handled by a complete-case analysis, which assumes that data are missing at random. If data are systematically missing, then it may be the case that early responders differ from late responders, and in extension that late responders are more similar to nonresponders. We will, therefore, explore the plausibility of the missing at random assumption by regressing the primary outcomes on the number of follow-up attempts needed before a response was recorded. To further explore the missing at random assumption, attrition will be investigated among study groups by comparing baseline characteristics between those who did and did not respond at follow-up.

For all models, coefficients of interest will be assessed for statistical significance using a null hypothesis testing approach, where tests will be 2-tailed at the .05 significance level. Alongside the null hypothesis tests, posterior distributions using a Bayesian approach will be calculated for each coefficient. Both significance tests and posterior distributions will create a basis for scientific inference [34].

Figure 1. Flowchart of the recruitment procedure.



The primary outcome (MHC-SF total score) is a discrete measure, which may be skewed; thus, we will regress this outcome on group allocation using negative binomial regression. Both unadjusted and adjusted models will be explored (adjusting for demographics, total MHC-SF, and mediator variables at baseline).

The 3 subscales of MHC-SF (emotional well-being, social well-being, and psychological well-being) are mean scores from Likert scale items, which should, because of the law of large numbers, tend toward normality. If by visual inspection it is deemed that the measures are skewed, we will use log transformation. We will regress the individual scores against group allocation using normal linear regression. Both unadjusted and adjusted models will be explored (adjusting for demographics and each score, respectively, and mediator variables at baseline).

Depression and anxiety scores from HADS will also be regressed against group allocation using negative binomial

regression. Both unadjusted and adjusted models will be explored (adjusting for demographics, depression, and anxiety, respectively, and mediator variables at baseline).

Mediators will be explored using a causal inference framework, where Monte Carlo methods are relied upon for inference. A total of 3 models will be created for each outcome measure: 2 that investigate the mediating factors on their own and a third model that incorporates all mediators at once.

Effect modification tests will be performed in all models to assess if any of the baseline characteristics moderate the effect of the intervention. Adjusted models will be primary.

Ethical Statement

The study has received ethical approval from the Regional Ethical Review Board, Linköping University, Sweden (Dnr 2018/519-32).

Results

Data will be collected between autumn 2018 and spring 2019. Results are expected to be published in 2020.

Discussion

Overview

This paper describes the design of a study that will evaluate the effect of a mobile phone–based intervention to increase positive mental health among university students. This study will add knowledge to the efficacy of a fully automated PPI. Previous research has investigated partly digital interventions and often only included single component interventions.

Strengths and Limitations

A potential challenge could be recruiting sufficient number of participants. According to our power analysis, we need just above 500 participants to achieve 80% power. By including some of the larger universities in Sweden and setting the recruitment period to 6 months, we believe that the study will recruit a sufficient sample.

A strength of the study is that it will investigate potential mechanisms of change. The proposed mediators in the study (positive emotions and cognitions) are based on a framework of mechanisms of positive interventions (the positivity-activity model). However, the challenge is how to measure these mediators in a reliable and feasible way. In a randomized controlled trial with already comprehensive baseline and follow-up questionnaires, it was not realistic to include lengthy validated instruments of, for example, positive emotions. A total of 2 single face valid items were therefore used to measure proposed mediators.

Another strength of the study is the use of the MHC-SF [2] to measure positive mental health. It is a validated comprehensive instrument including emotional and social well-being as well as psychological function. Positive mental health is a complex construct that requires the use of an instrument that captures both the hedonic and eudaimonic dimensions of well-being.

Conclusions

The promotion of positive mental health among the general population is increasingly becoming a core component of the public mental health agenda in Europe [17]. Mobile phone–based interventions could be a cost-effective choice for mental health promotion and an effective way to disseminate evidence-based interventions to larger audiences. However, more rigorous and larger studies that can clarify the evidence base in this area are needed [27]. This protocol describes a randomized controlled trial investigating a newly developed, fully automated, mobile phone–based intervention promoting well-being among university students. The trial can contribute to the knowledge on the feasibility and effect of the mobile phone–based intervention in promoting mental health.

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Authors' Contributions

KT developed the content of the intervention. MB undertook all the computer programming of the intervention. KT had the original idea for the study and designed the study together with MB. MB designed the statistical analysis plan and will perform all the data analyses. KT wrote the first draft of the study protocol to which MB then contributed. Both authors read and approved the final manuscript.

Conflicts of Interest

MB owns a private company that develops and distributes lifestyle interventions to be used in health care settings.

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Abbreviations

e-resource: electronic resource
HADS: Hospital Anxiety Depression Scale
MHC-SF: Mental Health Continuum Short Form
PPI: positive psychology intervention
SMS: short message service

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Protocol

Technology-Enabled Self-Monitoring of Chronic Obstructive Pulmonary Disease With or Without Asynchronous Remote Monitoring: Protocol for a Randomized Controlled Trial

Vess Stamenova[1], PhD; Rebecca Yang[1], MPH; Katrina Engel[2], RRT; Kyle Liang[1], MSc; Florence van Lieshout[1], BSc; Elizabeth Lalingo[3], RRT; Angelica Cheung[2], RRT; Adam Erwood[4], MMI; Maria Radina[5], MD; Allen Greenwald[5], MD; Payal Agarwal[1,6], MD; Aman Sidhu[7], MSc, MD; R Sacha Bhatia[1,8], MD, MBA; James Shaw[1,8], PT, PhD; Roshan Shafai[9], MD; Onil Bhattacharyya[1,6,8], MD, PhD

[1]Women's College Hospital Institute for Health System Solutions and Virtual Care, Women's College Hospital, Toronto, ON, Canada

[2]Respiratory Therapy Department, Markham Stouffville Hospital, Markham, ON, Canada

[3]Medicine, Care Transitions, Access & Flow, Respiratory Therapy, Markham Stouffville Hospital, Markham, ON, Canada

[4]Support Services & Transformation, Markham Stouffville Hospital, Markham, ON, Canada

[5]Centre For Respiratory Health, Markham Stouffville Hospital, Markham, ON, Canada

[6]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada

[7]University Health Network, Toronto, ON, Canada

[8]Women's College Hospital Research Institute, Women's College Hospital, Toronto, ON, Canada

[9]Hospital to Home and Community Medical Clinic, Markham Stouffville Hospital, Markham, ON, Canada

Corresponding Author:
Vess Stamenova, PhD
Women's College Hospital Institute for Health System Solutions and Virtual Care
Women's College Hospital
76 Grenville Street
Toronto, ON, M5S 1B2
Canada
Phone: 1 416 323 6400 ext 5112
Email: vess.stamenova@wchospital.ca

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide. Reducing the number of COPD exacerbations is an important patient outcome and a major cost-saving approach. Both technology-enabled self-monitoring (SM) and remote monitoring (RM) programs have the potential to reduce exacerbations, but they have not been directly compared with each other. As RM is a more resource-intensive strategy, it is important to understand whether it is more effective than SM.

Objective: The objective of this study is to evaluate the impact of SM and RM on self-management behaviors, COPD disease knowledge, and respiratory status relative to standard care (SC).

Methods: This was a 3-arm open-label randomized controlled trial comparing SM, RM, and SC completed in an outpatient COPD clinic in a community hospital. Patients in the SM and RM groups recorded their vital signs (oxygen, blood pressure, temperature, and weight) and symptoms with the Cloud DX platform every day and were provided with a COPD action plan. Patients in the RM group also received access to a respiratory therapist (RT). The RT monitored their vital signs intermittently and contacted them when their vitals varied outside of predetermined thresholds. The RT also contacted patients once a week irrespective of their vital signs or symptoms. All patients were randomized to 1 of the 3 groups and assessed at baseline and 3 and 6 months after program initiation. The primary outcome was the Partners in Health scale, which measures self-management skills. Secondary outcomes included the St. George's Respiratory Questionnaire, Bristol COPD Knowledge Questionnaire, COPD Assessment Test, and modified-Medical Research Council Breathlessness Scale. Patients were also asked to self-report on health system usage.

Results: A total of 122 patients participated in the study, 40 in the SC, 41 in the SM, and 41 in the RM groups. Out of those patients, 7 in the SC, 5 in the SM, and 6 in the RM groups did not complete the study. There were no significant differences in the rates of study completion among the groups (P=.80).

Conclusions: Both SM and RM have shown promise in reducing acute care utilization and exacerbation frequencies. As far as we are aware, no studies to date have directly compared technology-enabled self-management with RM programs in COPD patients. We believe that this study will be an important contribution to the literature.

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KEYWORDS

chronic obstructive pulmonary disease; remote consultation; remote monitoring; self-monitoring

Introduction

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition encompassing disorders such as emphysema and chronic bronchitis, which causes frequent exacerbations [1]. Exacerbations are events occurring in the natural course of the disease characterized by a change in dyspnea, cough, or sputum production. These changes must be beyond normal day-to-day variations, must have acute onset, and may warrant a change in medication. They also cannot be caused by another underlying condition [2].

COPD is the third leading cause of mortality worldwide [3] and accounts for 24% of hospital admissions and 24% of emergency department (ED) visits in Ontario, Canada; COPD is responsible for the highest percentage (18.8%) of 30-day ED readmissions in Ontario [4]. Canada-wide acute COPD exacerbations account for approximately Can $646 million to Can $736 million per year in hospital-based costs [5].

Self-Management

Reducing the frequency of exacerbations is both an important patient outcome and a major cost-saving approach. Self-management interventions have demonstrated some benefit in reducing the frequency of exacerbations and hospitalizations [6]. Self-management interventions often include some formal patient education, but in some cases, they simply involve sharing an action plan that the patient is expected to follow. An action plan is a list of instructions on what to do when a patient is experiencing an acute exacerbation of a chronic condition [7]. It is often personalized, generated by a health care provider, and meant to promote self-management [7]. A recent Cochrane review concluded that self-management approaches with action plans are associated with improvements in health-related quality of life (QoL) and a lower probability of hospital admission [8]. Studies have also shown that self-management approaches can increase patients' self-efficacy [9] and improve disease knowledge [10], but results are variable, with some studies reporting no effect [11].

The respiratory symptoms that patients often track as part of their action plan are generally subjective. Patients are instructed to refer to their action plan when their condition changes. Unfortunately, patients often act on their symptoms too late, when their condition has significantly deteriorated. For example, a study that surveyed patients with COPD across 14 countries [12], demonstrated that over a third of patients take a *wait and see* approach at the onset of exacerbations.

Technology-Enabled Remote Monitoring

With the advent of digital health and remote monitoring (RM) technologies, there is an opportunity to monitor patients regularly, providing greater insight than their subjective experience of symptoms alone. Traditional RM interventions may require patients to record physiological measures (eg, oxygen saturation and blood pressure) or subjective symptoms (eg, dyspnea and activity tolerance) or both on a daily basis [13,14]. In technology-enabled RM programs, the recorded information is stored on a cloud and may be transmitted to a health care provider on a regular basis. A health care provider can either actively monitor the data or refer to it only when needed. In a typical RM program, a clinical professional (eg, nurse and physician) reviews patient data on a regular basis (often once or twice a week) [13]. Health care providers can also be simply *alerted* or *notified* when a significant change is detected by the system or a specific threshold is exceeded [13]. In these instances, a clinical provider must call the patient to inquire about their status and provide guidance in care (potentially avoiding an in-person clinical visit). In some instances, patients are also called by a health professional once or twice a week, irrespective of their readings [15]. A number of studies have reported on the benefits of RM in COPD. For example, a recent Cochrane meta-analysis concluded that RM has shown promise in reducing acute care utilization and the number of exacerbations in COPD patients [16]. Studies of RM have reported lower emergency admission rates [17-19], up to 50% reductions in inpatient admissions [20], and reductions in length of stay [17,21]. RM can also improve patient knowledge of their condition and self-efficacy. For example, Rixon et al [22] showed that patients reported better emotional functioning and mastery 1 year after the implementation of an RM program.

Technology-Enabled Self-Monitoring

In a technology-enabled self-monitoring (SM) program, similar to an RM program, patients take their recordings daily but are not actively monitored by a clinician; however, a health care provider may have access to the data, if needed. If there is a change in clinical status, the alerts are communicated to the patient and automated instructions on how to deal with

exacerbations are provided [23]. This reduces the burden of work for the clinicians and has the potential to provide more timely feedback to the patients. However, it has been suggested that the effectiveness of RM programs may lie in the ability to interact one-on-one with a health care professional [15] and this aspect is completely removed in an SM program. It is, therefore, important to directly compare the 2 programs.

Study Objectives

Despite increasing evidence of the effectiveness of SM (some of which are technology-enabled) and RM programs, we are not aware of any studies to date that have directly compared the 2 programs. Many so-called *self-management* programs are remotely monitored [11,13,15,24] and as a result, the effectiveness of a technology-enabled self-management program alone, relative to a technology-enabled RM program, is not clear.

Given the lower staff cost and greater ease of implementing a self-management program, the goal of this study was to compare the effectiveness of implementing a technology-enabled SM program with a technology-enabled RM program in a COPD patient population compared with a standard care (SC) group.

We believed that both intervention programs will lead to improvements in self-management skills and respiratory symptoms relative to the SC program. In addition, patients in the RM group may gain more COPD knowledge than those in the SM group.

Methods

Study Design

This was an *open-label* randomized controlled trial of 6-month duration comparing 2 technology-enabled interventions relative to SC. Patients were randomized in a 1:1:1 ratio to 1 of 3 groups: an SM group, a self-managing and RM group, from here on called RM, and an SC group. Both SM and RM were technology-enabled. The study recruitment started in April 2018 and was completed in September 2018. Data collection ended in March 2019.

Participants

Eligibility Criteria

To be included in the study, patients needed to be aged 18 years and older and have a clinical diagnosis of COPD that had been established by their respirologist as per clinical guidelines [1]. Exclusion criteria included a diagnosis of other significant lung disease (eg, interstitial lung disease) or dementia, patients without Wi-Fi internet access in their home, inability to read English (required for filling out the questionnaires), participation in other RM programs, or inability to use the technology because of physical or cognitive impairment.

Study Setting

The study was conducted at an approximately 300-bed community-based hospital in Ontario. Recruitment was coordinated internally by a clinical study specialist, who was also a respiratory therapist (RT). Patients were recruited from an outpatient COPD clinic (Centre for Respiratory Health), the private practice of respirologists working at the same clinic, and an outpatient COPD rehabilitation program affiliated with the hospital.

Trial Intervention

Technology

The technology used in the study is the *Cloud DX Connected Health Kit* [25]. This specific technology was chosen as it was made by a local Ontario company; it was fully developed and on the market at the time of the study and it allowed for monitoring oxygen saturation.

All patients in the RM and SM groups were provided with the Cloud DX Connected Health Kit as a tool for SM and asynchronous RM. It comprised a custom tablet computer, a Pulsewave wrist cuff monitor, an oximeter, weight scale, and thermometer. The Pulsewave wrist cuff measures blood pressure, heart rate, and breathing rate and uniquely scans for 7 different cardiac anomalies, including missed beats, delayed beats, premature beats, and amplitude anomalies. All of these devices were optimized to work together, prepaired via Bluetooth, and ready to go out of the box and had been approved by the US Food and Drug Administration and Health Canada. Patients in the 2 intervention groups used the kit to record daily physiological and symptom scores by filling out a digital version of the COPD Assessment Test (CAT) [26] and modified Medical Research Council scale [27]. All Cloud DX data were transmitted to a cloud and patients and physicians interacted with it through a Web-based portal.

Intervention Procedures

Patients in the SM and RM group received the Cloud DX kit at the start of the trial and continued using it for 6 months. Patients in the SC group were given the opportunity to receive the kit at the end of the trial and use it free of charge and participate in a remote type monitoring program for 6 months (Figure 1).

Patients in the RM and SM group recorded their vitals and symptoms with the Cloud DX platform every day and were provided with a written version of a COPD action plan (Figure 2).

This document comprised a chart that instructed patients on what to do if their readings fell outside the predetermined thresholds. These values were determined on an individual basis by the clinical study specialist in consultation with the patient's respirologist. The action plan included actions, such as contacting the clinic, filling out a prescription, or going to the ED. Patients in the RM and SM groups also had the option to email or call the clinic with any nonemergency questions they might have had.

Figure 1. Patient flow through each arm of the study. A total of approximately 800 patients were screened for eligibility to obtain the final sample of 122 participants.

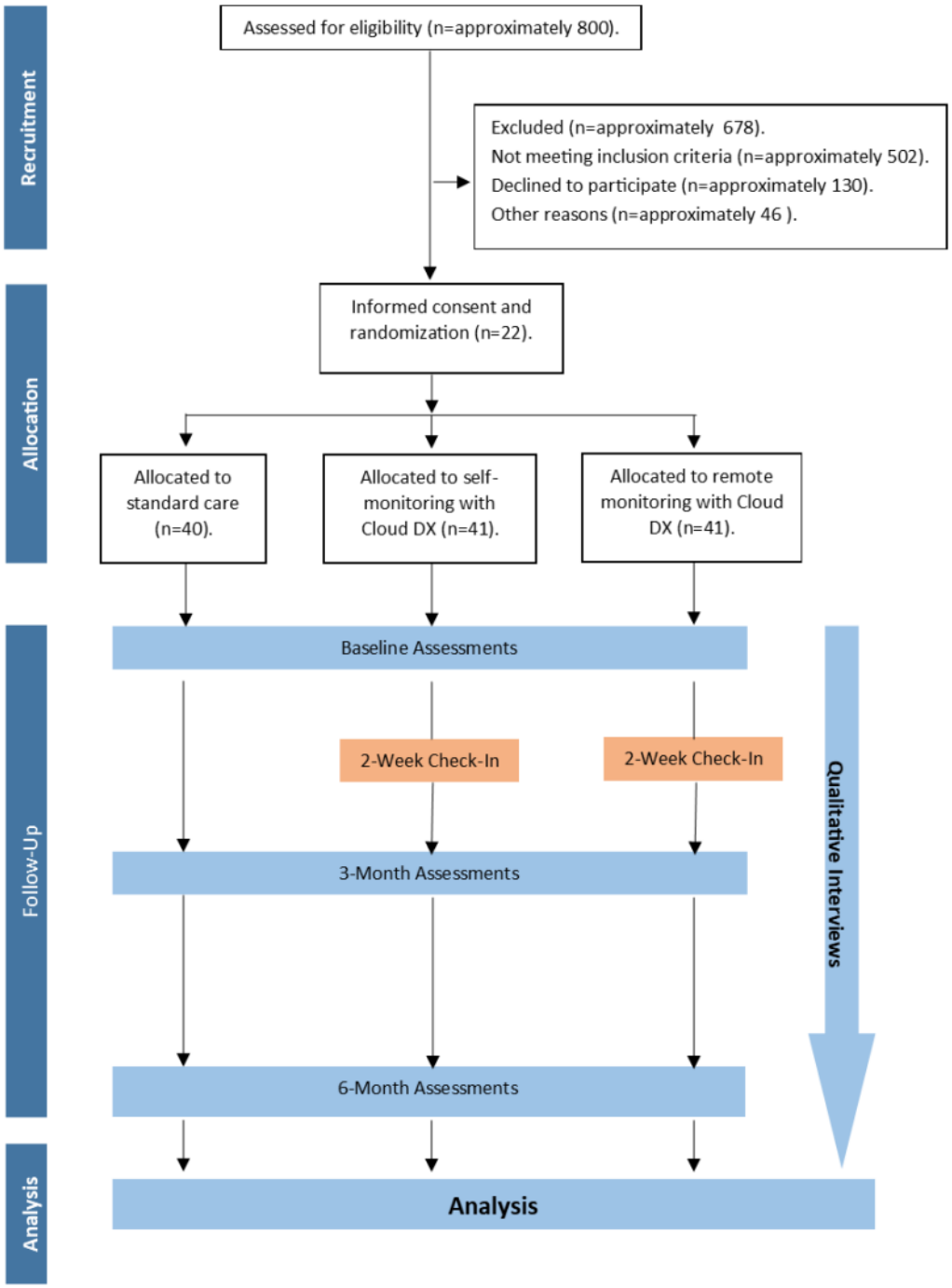
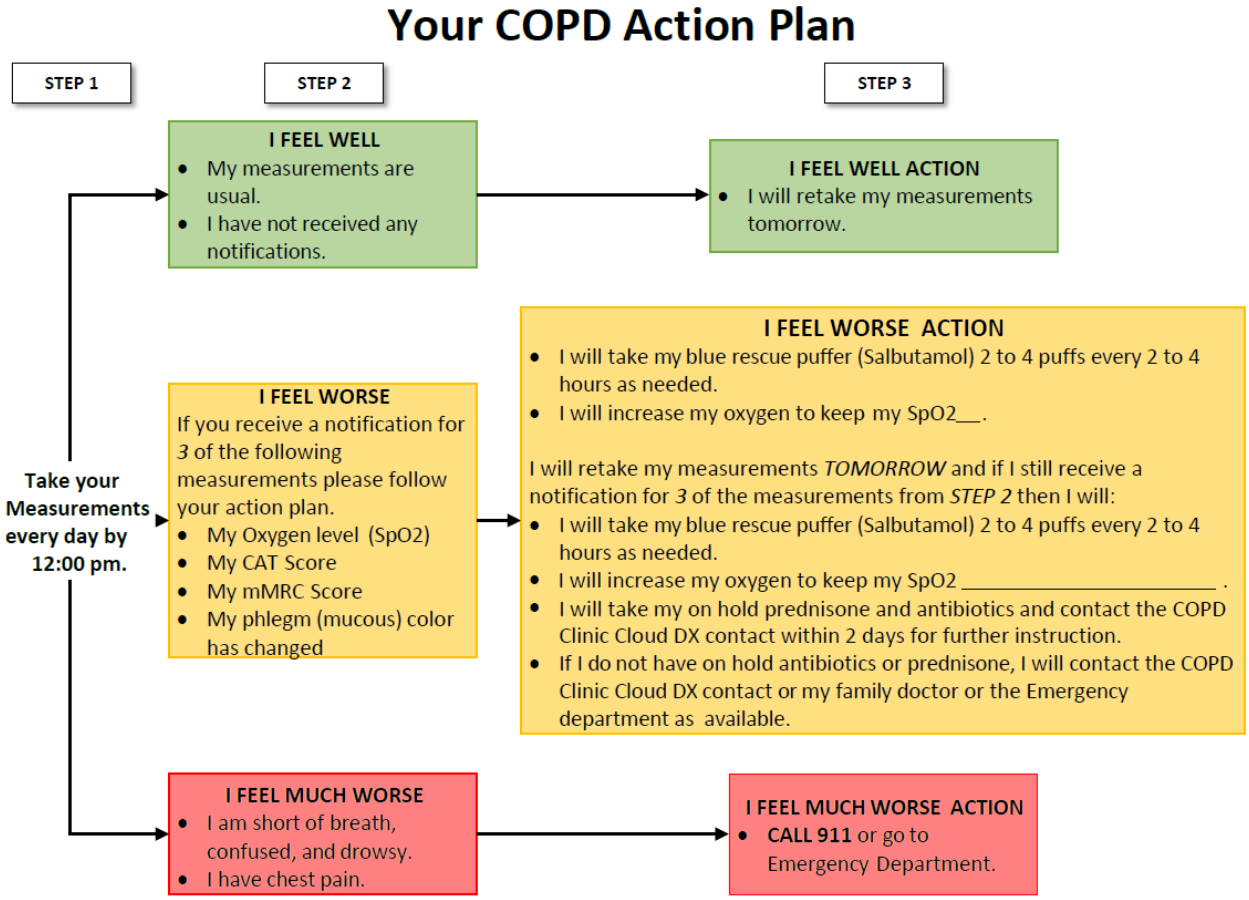


Figure 2. The chronic obstructive pulmonary disease action plan given to participants in the self- and remote monitoring group. The action plan was provided on a piece of paper and patients were asked to refer to it when needed. COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; SpO2: peripheral oxygen saturation.



For patients assigned to the RM group only, if a patient's readings fell outside the predetermined thresholds, a notification was sent to both the clinical study specialist and patient through email. Whenever readings exceeded a predetermined threshold, the notifications, along with all other vital signs and symptoms, were reviewed by the clinical study specialist and responded to when clinically indicated. Generally, patients in the RM group received a follow-up call from the clinical study specialist whenever their readings exceeded thresholds twice or more within 2 days. The follow-up calls were completed only Monday to Friday, during regular clinic business hours (8:30 am-4:30 pm). An attempt to complete the follow-up call was done within 24 hours of receiving the notification. If the patient was unavailable, a message was left to call the clinical study specialist back.

The RT also checked on patients in the RM group once a week irrespective of the value of the vitals. The purpose of the call was to check on the patients, prompt action plan use, and act as an educational opportunity to teach the patient about their COPD.

Notifications from the SM group were only sent to the patient. Although the notifications were recorded and were visible to the clinical study specialist, their notifications were not actively monitored or acted upon, unless a patient initiated contact with the clinic.

Aside from these regular (primary) notifications, all patients in the RM and SM group had secondary threshold levels preset by the site investigator for oxygen levels, heart rate, and blood pressure. These were extreme measures that required immediate assistance. Cloud DX staff monitored these levels (as they normally currently do and as is required by Health Canada regulations). In the event that a patient exceeded a secondary threshold, they were contacted by Cloud DX to ensure patient safety and were advised to contact emergency services if they were feeling unwell. Events that required intervention, and were not a result of a technical or reading error, were communicated back to the clinical study specialist. Cloud DX monitored these readings Monday through Friday, 8:30 am to 8:00 pm, and weekends and holidays 9:00 am to 1:00 pm.

All physiological and symptom recordings taken by the patients were transmitted to a secure website where they could be accessed by a predetermined set of the patient's clinical care providers. The clinical study specialist monitoring the data for the RM group could access the data by looking at the clinician dashboard in this central Web portal, accessible on any personal computer, Mac, or mobile device. Patients in both the SM and RM groups who had not entered data for a week were contacted by Cloud DX staff to inquire whether there was still interest in participation.

Patients in this SC group were not provided with a technology or an action plan, as the action plan was based on vitals and symptoms. This group received the standard care from the respiratory clinic including routine in-person follow-up appointments and access to certified respiratory educator. Some patients may have had an action plan given to them by their respirologists before joining the study, but that action plan was not the same as the one used in the RM and SM groups and was strictly based on subjective symptoms.

The initial visit for RM and SM group patients took 2 hours to allow the obtainment of consent, an introduction of the kit, and baseline survey completion. The initial visit for SC patients took about 1 hour. Patients in the SM and RM groups were also contacted by the clinical study specialist 2 weeks after receiving their kit to reassess the appropriateness of the thresholds. If a revision of the thresholds was required, the clinical study specialist revised it with the respirologist's approval.

All patients were advised to go to the ED, as they would normally, if they felt the need to at any point in time. Patients were also informed that data were not monitored 24 hours and 7 days a week and to respond to their clinical needs as they would normally do outside of the study.

All patients completed 3 assessments: at baseline, 3 months, and 6 months on a series of questionnaires. Visits 2 and 3 could be done in-person or remotely (on the Web or over the phone). The surveys were available on the Web through a REDCap (Research Electronic Data Capture), Vanderbilt University, electronic data capture tool hosted at Women's College Hospital [28].

Outcomes

Primary Outcome

The primary outcome of interest was measurement of change in the Partners in Health (PIH) scale [29]. The PIH scale is a validated scale measuring the current status of self-management, with items on knowledge of the condition and skills to monitor and respond to symptoms. This scale was chosen as a primary, as we believed that both interventions could lead to self-management improvement.

Secondary Outcomes

The secondary outcomes included measures of general respiratory health, COPD knowledge, and health utilization measures. QoL and respiratory symptoms were assessed with the St. George Respiratory Questionnaire (SGRQ) [30]. The SGRQ is an index designed to measure and quantify health-related status in patients with chronic airflow limitation. It has been shown to correlate well with the established measures of symptom level and disease activity [31]. The first part (*Symptoms*) evaluates symptomatology, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of attacks of breathlessness or wheeze. The second part has 2 components: *Activity* and *Impacts*. The *Activity* section addresses activities that cause breathlessness or are limited because of breathlessness. The *Impacts* section covers a range of factors including influence on employment, being in control of health, panic, stigmatization, the need for medication, side effects of prescribed therapies, expectations for health, and disturbances of daily life.

The Bristol COPD Knowledge Questionnaire [32] is a measurement of COPD patients' disease knowledge level. It comprises 13 subscales, each of which assesses a topic of COPD knowledge: (1) epidemiology, (2) etiology, (3) symptom, (4) breathlessness, (5) phlegm, (6) infections, (7) exercise, (8) smoking, (9) vaccination, (10) inhaled bronchodilators, (11) antibiotics, (12) oral steroids, and (13) inhaled steroids. This test has been used in the past to assess patients' knowledge of COPD [33].

The CAT [26] is a reliable and standardized questionnaire for assessing and monitoring COPD.

Patients were also asked to self-report at baseline, 3 months, and 6 months, the following measures for the past 3 months: the number of COPD-related ED presentations, number of COPD-related admissions to a hospital, the length of stay for all COPD-related admissions (in days), number of exacerbations (episodes in which antibiotics or steroids were prescribed or hospital/clinic visit because of a respiratory issue), number of COPD-related visits to family doctor, number of COPD-related nurse contacts, self-reported use of medication, and self-reported smoking cessation. The number of contacts/calls to the outpatient clinic and deaths were tracked and reported by the clinical study specialist. In addition, hospital admission data and ED use from the local hospital were also obtained.

Finally, vendor-recorded usage data were also documented and sent for analysis at the end of the trial. This included frequency of recordings for oxygen and blood pressure and the number of times thresholds were exceeded.

Data Analysis Plan

Sample Size

One self-management study [34] examined the effects of a telephone self-management program in COPD patients and used both the PIH scale and SGRQ. The effect size of the change over a 6-month period between the control and the intervention group was 0.42 for the PIH and −0.27 for the SGRQ. Assuming an alpha=.05 and correlation between repeated measures of 0.85, a total sample of 82 for a comparison between one of the intervention groups and the SC group at baseline and 6 months (41 patients per group) will produce a power of 0.97 for PIH and 0.71 for the SGRQ. Unfortunately, we did not have the resources to increase the sample size to account for attrition.

Recruitment

All eligible patients who were seen at the outpatient COPD clinic within the past year (Centre for Respiratory Health) were contacted for participation and had an equal opportunity to participate (random sampling). Some patients who were seen by the respirologists working outside that clinic were also considered for participation. Some patients were also referred from an affiliated outpatient COPD rehabilitation program that was coordinated by RT working at the COPD clinic. The patients outside the clinic were chosen either by the respirologist/RT as patients that may benefit from the program or self-elected into

the study after hearing word of mouth about the study from somebody else.

All eligible patients were contacted by phone, at an appointment, or at the hospital's exercise rehab program by a clinical staff member (respirologist or RT) who briefly described the technology, provided patients with information about the trial, and requested permission to pass the patient's information to the clinical study specialist. At this time, the consent form (see Multimedia Appendix 1) was provided to allow patients enough time to consider participation. The clinical study specialist later called the patients to further inquire about their interest in participating and describe the study. The patients who were still interested in the study were scheduled for their baseline evaluation, when the informed consent was obtained, group allocation was revealed, baseline questionnaires were completed, and the Cloud DX kit was provided to them (if in SM or RM group). Patients could split that session into 2, if they felt it was too much for 1 visit.

Randomization

Patients were randomized into 1 of the 3 groups using a Web-based random number generator [35]. The generator produced a list of 123 unique numbers from 1 to 123. This list was aligned to a list of group categories. The numbers represented the sequential recruitment of the participant and their corresponding participant ID. The group in which each patient ID belonged was listed on a piece of paper and entered into a sealed envelope with the participant ID on the envelope to allow for allocation concealment from the clinical study specialist who did the recruitment. After obtaining informed consent, the clinical study specialist opened the envelope and determined the group in which the patient was assigned. Once the envelope was opened, both the clinical study specialist and the patient were unblinded to which treatment group the patients were assigned to.

Statistical Analysis

All quantitative continuous data will be analyzed by conducting a between-group repeated-measures analysis of variance analyses comparing the scores at baseline, 3 months, and 6 months follow-up assessments of each group. A significant interaction effect between group and time of assessment will indicate that the effect varies per group. Post hoc comparisons will be run to examine changes in outcome between time points. We will also run within-group comparisons, examining differences in performance between each assessment at baseline, 3-month, and 6-month follow-up. Comparison of withdrawal between groups will be conducted and pairwise deletion on missing data will be done (or regression imputation if significant amount is missing).

Study Significance

The use of technology has the potential to provide clinical marker feedback to the patient and the clinical care provider (RM group), resulting in better disease control and improved self-management skills and QoL. Both programs have the potential to reduce face-to-face visits (outpatient and inpatient admissions). The RM group may be more effective in that regard because of its ability to directly communicate with patients, but it is also more costly in terms of staff time and institutions may incur some additional liability, so it is important to quantify any additional benefit it may provide. The goal was to empower patients and improve their engagement and self-management skills, leading to faster resolution of their health concerns and resulting in fewer complications that may lead to outpatient clinic visits, ED visits, and inpatient admissions. This would increase institutional capacity to offer extended health care services to more patients and improve the overall quality of health care delivered.

Qualitative Evaluation

A qualitative study about the implementation of the SM and RM programs was embedded during the second half of the study. Interviews were conducted with 8 patients (SM:RM=4:4), 2 caregivers (SM:RM=1:1), 5 health care providers, and 3 hospital administrators/managers who participated in the study or were involved in the implementation of the technology in the clinic. For the patients and health care workers, we aimed to interview both high users and lower users of the technology.

The goal of the qualitative portion was to provide insights in the implementation of the Cloud DX kit in this setting and explore possible improvements for future implementation. Given that technology-enabled programs have not been used in this setting, it was important to understand what worked and what did not and establish what factors could improve the chances for scale-up of the program. The framework tool+team+routine [36] was used for designing the interview guide and analyzing the results. This framework focuses on a *service design* [37] approach to digital health implementation and investigates the changes that need to be made to the tool, team, and routine of everyone involved to create a sustainable delivery of care with successful adoption of the technology. The interviews were audio recorded, transcribed verbatim, and analyzed using thematic analysis [38,39]. The first 2 interviews were coded by multiple researchers and codes were compared to make up the code book for the rest of the interviews to minimize researcher bias.

Ethics and Dissemination

The study was approved by the Markham Stouffville Hospital and Women's College Hospital Research Ethics Boards in Ontario, Canada (Protocol version: 1.8, December 7, 2018) (see Multimedia Appendix 2). The study was also retrospectively registered with ClinicalTrials.gov (NCT03741855). Once the results of the study are available, the study will be submitted for publication in a peer-reviewed medical journal and presented at national and international conferences. Significant protocol amendments will be reported to all relevant parties.

Patient and Public Involvement

During the initial planning stages of the study, we used a co-design approach in the development of the intervention. Patients were given access to the technology for 2 weeks and were subsequently interviewed about their experiences. Health care providers were also interviewed about their current models of care and experience with the technology. The goal of this process was to establish if technology met the needs of its users (patients and health care providers) and determine whether any

modifications to the technology and the service it provided were needed. Modifications to both service and technology were done in response to this feedback. Some of this feedback was also used to inform decisions about primary and secondary outcome selection.

Patient advisers were not involved directly in the development of the research question and outcome measures or recruitment. The burden of the intervention was assessed by the research ethics boards who have public member representatives. Any participants interested in receiving information about the results of the study will be provided with a summary once the results are available.

Results

Data collection is now complete. A total of 122 patients participated in the study, 40 in the SC, 41 in the SM, and 41 in the RM groups. Out of those patients, 7 in the SC, 5 in the SM, and 6 in the RM group did not complete the study because of various reasons (8 withdrew from the trial for various reasons, 6 were noncompliant with their readings, 4 deceased, and 1 dropped because of the technology being difficult to use). There were no significant differences in the rates of study completion among the groups (P=.80). We expect the analyses to be completed early in summer and the final version of the report to be submitted for publication before the end of summer.

Discussion

Study Contributions

As the digital health field grows in popularity and practice, there are increasing numbers of programs that use digital self-management and RM technologies. Both SM and RM have shown promise in reducing acute care utilization and exacerbation frequencies [6,16]. As far as we are aware, no studies to date have directly compared technology-enabled SM programs with technology-enabled SM plus RM programs. As there is a significant cost associated with having a clinical provider actively monitor the patients' recordings, it is important to evaluate the impact of a clinician monitoring the data and regularly checking in with patients. This impact will be evaluated as it relates to self-management behaviors, COPD disease knowledge, and respiratory status.

Strengths

Some of the strengths of this study include the randomized controlled trial design, the ability to not only directly compare the 2 intervention methods but also compare them with SC. Another advantage is that the technology we used is relatively well established and less likely to malfunction in routine use.

Limitations

The disadvantage of the design was the relatively short assessment period of 6 months. Unfortunately, the funding program that funds the study limited the duration of the intervention. It is possible that certain effects (eg, on health system utilization) will only be detectable over a longer period of time. Finally, the funding available also limited the sample size, and technology interventions sometimes face high dropout rates. Both of these pose a risk to us being able to detect an effect. We have powered the study appropriately for the primary outcome, but it is possible that the secondary outcomes are not adequately powered to rule out an effect. Despite these limitations, we believe that this study will be an important contribution to the literature because it will constitute the first direct comparison of an SM and an RM program.

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Authors' Contributions

VS, RY, KE, FvL, PA, AS, RSB, JS, RS, and OB designed the study and selected outcome variables. VS, RY, KE, EL, AC, AE, PA, AS, JS, RS, and OB interpreted pilot investigations that guided the final design of the trial. VS, RY, KE, EL, AC, AE, MR, AG, PA, AS, RSB, JS, RS, and OB designed the intervention. KE, KL, FvL, AC, MR, and AG contributed to data acquisition and recruitment. VS, KL, and FvL wrote the initial draft. VS, RY, KE, KL, FvL, EL, AC, AE, MR, AG, PA, AS, RSB, JS, RS, and OB contributed to paper revisions. VS, RY, KE, KL, FvL, EL, AC, AE, MR, AG, PA, AS, RSB, JS, RS, and OB approved the final version of the paper and have agreed to be personally accountable for the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Approved informed consent form for study participants.
[PDF File (Adobe PDF File), 251KB - resprot_v8i8e13920_app1.pdf]

Multimedia Appendix 2

Approved full research protocol for randomized controlled trial (protocol version: 1.8, 7 December 2018).
[PDF File (Adobe PDF File), 231KB - resprot_v8i8e13920_app2.pdf]

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Abbreviations

CAT: COPD Assessment Test
COPD: chronic obstructive pulmonary disease
ED: emergency department

PIH: Partners in Health
QoL: quality of life
RM: remote monitoring
RT: respiratory therapist
SC: standard care
SGRQ: St. George Respiratory Questionnaire
SM: self-monitoring

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Protocol

A Systematic Framework for Analyzing Patient-Generated Narrative Data: Protocol for a Content Analysis

Maryam Zolnoori[1], PhD; Joyce E Balls-Berry[1,2], PhD; Tabetha A Brockman[3,4], MA; Christi A Patten[3,4], PhD; Ming Huang[1], PhD; Lixia Yao[1], PhD

[1]Department of Health Sciences Research, Mayo Clinic, Rochester, MN, United States

[2]College of Medicine and Science, Mayo Clinic, Rochester, MN, United States

[3]Community Engagement Program, Center for Clinical and Translational Science, Mayo Clinic, Rochester, MN, United States

[4]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, United States

Corresponding Author:
Lixia Yao, PhD
Department of Health Sciences Research
Mayo Clinic
200 First Street SW
Rochester, MN,
United States
Phone: 1 507 293 7953
Email: Yao.Lixia@mayo.edu

Abstract

Background: Patient narrative data in online health care forums (communities) are receiving increasing attention from the scientific community for implementing patient-centered care. Natural language processing (NLP) methods are gaining more and more attention because of the enormous data volume. However, state-of-the-art NLP still cannot meet the need of high-resolution analysis of patients' narratives. Manual qualitative analysis still plays a pivotal role in answering complicated research questions from analyzing patient narratives.

Objective: This study aimed to develop a systematic framework for qualitative analysis of patient-generated narratives in online health care forums.

Methods: Our systematic framework consists of 4 phases: (1) data collection, (2) data preparation, (3) content analysis, and (4) interpretation of the results. Data collection and data preparation phases are constructed based on text mining methods for identifying appropriate online health forums for data collection, differentiating posts of patients from other stakeholders, protecting patients' privacy, sampling, and choosing the unit of analysis. Content analysis phase is built on the framework method, which facilitates and accelerates the identification of patterns and themes by an interdisciplinary research team. In the end, the focus of interpretation of the results phase is to measure the data quality and interpret the findings regarding the dimensions and aspects of patients' experiences and concerns in their original contexts.

Results: We demonstrated the usability of the proposed systematic framework using 2 case studies: one on determining factors affecting patients' attitudes toward antidepressants and another on identifying the disease management strategies in patient with diabetes facing financial difficulties. The framework provides a clear step-by-step process for systematic content analysis of patient narratives and produces high-quality structured results that can be used for describing patterns or regularities in patients' experiences, generating and testing hypotheses, and identifying areas of improvement in the health care systems.

Conclusions: The systematic framework is a rigorous and standardized method for qualitative analysis of patient narratives. Findings obtained through such a process indicate authentic dimensions and aspects of patient experiences and shed light on patients' concerns, needs, preferences, and values, which are the core of patient-centered care.

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KEYWORDS

social media; online social networking; patient-centered care; qualitative research; framework method; inductive approach; deductive approach; text mining

Introduction

Online health forums (communities) are increasingly accessible and convenient platforms for patients and caregivers to share health care experiences together with concerns of diagnosis, treatment, and outcomes. Almost 30% of the US population actively share and discuss health-related experiences on various online health forums, such as askapatient.com, patientslikeme.org, and dailystrength.org [1]. Patient-reported health care experiences in a narrative format on the internet are a valuable data source for implementing patient-centered care [2].

There are 2 methods for analyzing patient-generated narrative data: natural language processing (NLP) and qualitative content analysis. NLP is a set of methods and techniques to process human language components, such as identifying sentence structure and recognizing sentence meaning as humans do [3]. NLP algorithms build on statistical methods to infer patterns in data. The algorithms usually need an annotated dataset (train dataset) for learning meaningful patterns and concepts to make predictions about new data [4]. In the context of patients' narratives, NLP is mostly used for clustering health-related messages [5], identifying the topics of concern [6], and recognizing the opinions and sentiments of patients toward different topics. With the fast-growing volume of patient-generated narratives in online health forums, NLP has been gaining increasing attention. However, the available NLP techniques are not able to provide a high-quality understanding of the text, such as identifying patients' functional problems because of colloquial language, word ambiguity, and layperson terms [7,8].

The second method for analysis of patient-generated narratives is qualitative content analysis. Qualitative content analysis is a research method designed to identify the thematic structure of text documents by subjectively interpreting the context of the text [9]. This process is conducted through a systematic classification process of coding and identifying themes and patterns in the text. Unlike the NLP algorithms, this method can provide a deep insight into textual data for identifying patterns and various aspects of the textual content. However, this method is usually applied on a small sample of data because of the manual process of analysis. In the context of patient narrative data, qualitative content analysis has been used to identify meaningful patterns and themes in patients' discussions in online health care forums to answer complex research questions such as factors affecting patients' attitudes toward antidepressants and contributions of MD Anderson's Facebook group to patient's cancer experience.

In this study, we propose an efficient and cost-effective systematic framework built on text mining and qualitative content analysis approaches for analyzing patients' narratives. This framework comprises 4 phases: (1) data collection, (2) data preparation, (3) content analysis, and (4) interpretation of findings. Data collection and data preparation phases utilize text mining methods to facilitate and accelerate the process of data collection and preparation for content analysis. The content analysis phase utilizes the framework method [10] and the deductive-inductive approach to facilitate the process of data analysis and interpretation of the findings. Overall, the proposed systematic framework offers a comprehensive approach to identify dimensions and aspects of patients' narratives in online health care forums in an efficient manner.

In this study, we first provide a brief introduction to the framework method [10] and content analysis and theme generation approaches with examples from research conducted using patient-generated narratives. Next, we describe the proposed framework and demonstrate its applicability for analysis of patient narratives using 2 case studies: one on determining factors affecting patients' attitudes toward antidepressants using data from askapatient.com [11] and another on identifying the disease management strategies in patients with diabetes facing financial difficulties using data from 4 diabetes-focused forums.

The Framework Method for Content Analysis

The framework method was developed in the qualitative research unit at the National Centre for Social Research in the United Kingdom in 1980 for analyzing narrative data related to policy [10] and later adopted in other fields, including health care. It identifies themes in data systematically, where each theme represents a semantic topic. More specifically, the framework method builds a matrix structure with each piece of narrative data (eg, a patient post or a sentence) stored in a row and each identified theme in a column. Using this structure, researchers can cluster narrative data around identified themes and identify the relationships between themes (see Figure 1). This framework provides a holistic, descriptive picture of a reasonably large sample of data.

Figure 1. Structure of the framework method. Sentences from patient posts (unit of analysis) organized in the rows and themes (adverse drug reactions) organized in the columns. Value "1" indicates to which theme a sentence was assigned.

comment_Id	drug_id	sentence_index	sentences	ADR	WD	EF	INF	PPI-P	PPI-N	KN	SS	ADR-PA	ADR-NA	WD-PA	WD-NA	Others
1	EffexorXR.1	1	Total nightmare.										1			
1	EffexorXR.1	2	This was arguably the worst period of time in my life.										1			
1	EffexorXR.1	3	It made me so mentally ill I almost ended up in a psych ward.	1												
1	EffexorXR.1	4	Stay away from this if you can!													1
1	EffexorXR.1	5	I lost weight considerably and shook all the time.	1												
1	EffexorXR.1	6	I had terrible anxiety the whole time, the worst kind of anxiety I've ever experienced.	1			1						1			
1	EffexorXR.1	7	Also tardive diskenesia was becoming very prevalent.	1												
1	EffexorXR.1	8	Tobacco cravings were rampant.	1												
1	EffexorXR.1	9	I never felt at ease or comfortable, I was constantly on edge and wanted to cry.	1												
1	EffexorXR.1	10	Please be careful if you are taking this, o													1
2	EffexorXR.2	1	Sleepy, constipated, unable to orgasm, felt "out of body" most of the time.	1												
2	EffexorXR.2	2	Some improvement in mood but not worth it, at all.			1							1			
2	EffexorXR.2	3	Withdrawal is difficult and unpleasant.										1			
2	EffexorXR.2	4	Would not recommend this drug to anyone.													1
3	EffexorXR.3	1	Extreme irritability, weight gain and sleepless are just a few side effects of this horrible drug.	1									1			
3	EffexorXR.3	2	Sure it helps depression because it makes you not give a rats ass about anything!	1		1										
3	EffexorXR.3	3	I was on 225 mg and have weaned down to 37,5.													1
3	EffexorXR.3	4	The only way I can sum it up is to say I wish I could be put to sleep for a month or so while this gets out of my system.										1			
3	EffexorXR.3	5	Horrible Horrible Horrible													1
4	EffexorXR.4	1	I tried to kill myself witch mad no sense since I LOVE MY LIFE!	1												
4	EffexorXR.4	2	The effexor worked great at first and then slowly i started to sleep more and feel more and more depressed, I also started having weird behavior.	1		1	1									
4	EffexorXR.4	3	I never tried to hurt myself before this drug, o	1			1									
5	EffexorXR.5	1	constipation, drastic mood swings, 100% helped my anxiety and panic.	1		1										
5	EffexorXR.5	2	didnt do much for the depression.				1									
5	EffexorXR.5	3	This drug is the devil.										1			
5	EffexorXR.5	4	Ever try getting off of it?													1
5	EffexorXR.5	5	You would think you were going through heroin withdrawals.												1	
5	EffexorXR.5	6	Im lucky I didnt die b/c I just stopped cold turkey one day and the brain zaps puking and overall feeling you get is like no other.		1											
5	EffexorXR.5	7	I will never touch an antidepressant again.												1	
5	EffexorXR.5	8	Just to think that I went through all that physical and mental anguish to get off a drug.		1										1	
5	EffexorXR.5	9	it could not be safe to take on a daily basis													1

Themes in the framework method are generated through deductive, inductive, or a combination of the deductive-inductive approach. The selected approach depends on the research question, the study's aim, and the available knowledge about the phenomena under study. The deductive approach is used when the aim of the study is to retest the existing model, concept, or knowledge in a new context [12]. In the context of patient narratives, Latvala et al and Kasila et al used the inductive approach to identify meaningful concepts [13,14]. When the available knowledge about phenomena under study is limited, the inductive approach is used to identify new themes. For example, Zolnoori et al, Hilliard, and Sutton et al used the inductive approach to identify meaningful patterns and themes in patients' discussions in online health care forums [15-17]. Finally, the deductive-inductive approach is used when researchers wish to test the existing knowledge in a new context and leave space to discover new aspects of the data that were not covered by existing knowledge. For example, Zolnoori et al used the deductive-inductive approach to test hypotheses concerning patients' attitudes toward antidepressants using patients' drug reviews in askapatient.com [11].

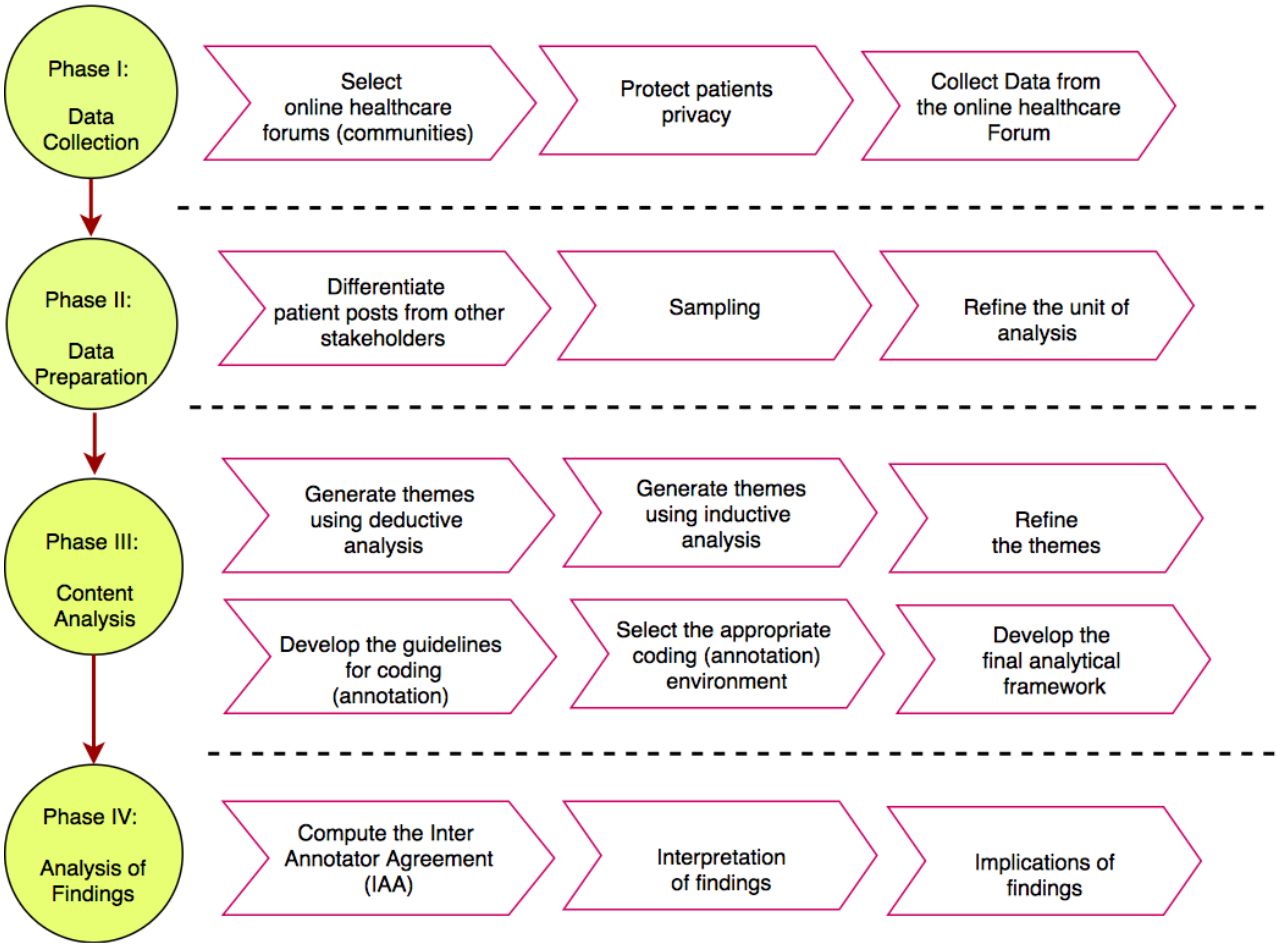
Methods

Overview

Building on our previous experiences and lessons learned from the content analysis of patients' narratives, we propose a systematic framework to address the subjective nature of patients' narratives [11,18-20]. This framework integrates text mining methods, the framework method, and deductive-inductive approach for content analysis and is composed of 4 main phases: (1) data collection, (2) data preparation, (3) content analysis, and (4) interpretation of the results. During the data collection phase, relevant health forums are selected regarding the aim of the study. The data preparation phase uses text mining methods for (1) distinguishing patients' comments from other stakeholders (caregivers and clinicians), (2) sampling patients' narratives, and (3) preparing the unit of analysis. The focus of content analysis phase is on the framework method and the deductive-inductive approach to generate a structured matrix that presents various aspects of patients' narratives. Finally, the focus of interpretation phase is on measuring quality criteria, validation, and interpretation of findings. Figure 2 shows a schematic view of the systematic framework.

In the following sections, we demonstrate the implementation of each step of this systematic framework using 2 studies: (1) a case study that identified factors affecting patients attitudes toward antidepressants; we use the short title *attitude to antidepressants* to refer to this case study [11] and (2) a case study that analyzed the strategies and solutions of patients with diabetes facing financial difficulties to access medications and supplies; we use the short title *access to diabetes medications* to refer to this case study.

Figure 2. A schematic view of the systematic framework designed for content analysis of patient narrative data.



Phase I: Data Collection

The data collection phase of the systematic framework included selecting health forums, protecting patients' privacy, and collecting data from these health forums.

Selection Health Forums for the Study

Health forums vary in covering patients' experiences with the health care system. Researchers can select a health care forum for their study using (1) description of the forum or community, (2) initial analysis of randomly selected posts, and (3) analysis of medical concepts using text mining tools such as MetaMap [21] or clinical Text Analysis and Knowledge Extraction System [22]. Researchers may choose multiple forums for a study to reduce the risk of potential bias in the findings that may occur because of an unbalanced sampling of patient experiences in a health forum. However, determining the number of forums depends on the aim of the study and the level of heterogeneity in patient experiences. For example, for the study *attitude to antidepressants*, we used only 1 forum askapatient.com because our initial content analysis using MetaMap [17] showed that this forum covers a wide range of antidepressants' side effects and potential factors affecting patients' attitudes toward antidepressants.

Patients' Privacy in the Health Forums

Although data in the forums are mostly anonymous and publicly available, further protection of patient's privacy and requesting permission from owners of the data collection are recommended. Researchers need to submit the institutional review board's (IRB's) study approval to the affiliated institute. The IRB submission usually receives an exemption. In addition, to further protect patient privacy, deidentification of the data is recommended. For example, in both projects, we formulated regular expressions to eliminate emails, phone numbers, and URLs from posts. For the project *attitude to antidepressants*, we sought IRB approval through the University of Wisconsin-Milwaukee, and for the project *access to diabetes medications*, we sought IRB approval through the Mayo Clinic.

Data Collection From an Online Health Forum

Patient posts in the online health forums are mostly stored in the HTML format. To collect these data, the research team may use the application programming interface (API) specifically developed for the forum or community. If the API is not available, the research team may customize the existing open-source Web crawlers or develop a new one to collect data. For example, we used Beautiful Soup [23], a python package for parsing HTML and XML documents, to develop a Web crawler. Please see Multimedia Appendix 1 for the definition of HTML, API, Web crawler, Python package, and XML.

Phase II: Data Preparation

Data preparation phase consists of 3 steps: differentiating patient posts from other stakeholders, sampling, and defining the unit of analysis.

Differentiating Patient Posts From Other Stakeholders

Patients' interests and perspectives on treatment are different from that of clinicians and caregivers who share their experiences and concerns for their patients in online health forums. Distinguishing patients' experiences from other stakeholders can be achieved by utilizing text mining approaches such as unsupervised algorithms for text clustering [24] (eg, density-based spatial clustering of applications with noise, expectation-maximization, or agglomerative hierarchical clustering). For example, Lu et al leveraged the expectation-maximization algorithm for differentiation between patient posts from caregivers and clinicians [5]. To improve the performance of the clustering algorithms, selecting a proper feature such as writing style–based features (eg, lexical and syntactic) [25,26] and content-specific features (eg, kinship terminology, Unified Medical Language System [UMLS] semantic types and concept IDs, and n-grams) [26,27] is useful. See Multimedia Appendix 2 for more information about kinship terminology and UMLS.

Sampling

Having a representative sample of online forums content is pivotal for statistical reliability and generalizability of the findings. To increase the likelihood of having a representative sample, the research team may utilize retrieval methods such as phrase-based vector space model [28,29] or knowledge-based query expansion method [30]. The retrieval methods are particularly useful when the forums do not have a built-in system for filtering specific information, and the content covers a wide range of patients' experience.

If the size of retrieved relevant patient posts is extremely large, probability sampling methods (such as simple random sampling, stratified random sampling, or cluster sampling) are useful to obtain a robust sample size *[31]*. If the document retrieval methods do not retrieve relevant patient posts for the research question, the research team may use nonprobabilistic samplings, such as *convenience sampling or judgmental sampling [31]*.

Determining the sample size is another concern in content analysis studies. There is no single formula for determining the sample size. The size of the sample is a factor of time and financial sources and data heterogeneity. Researchers may use the standard sampling formula for computing the sample size [32]. As an example of sample size calculation, please see Multimedia Appendix 3 [33,34].

Defining the Unit of Analysis

A unit of analysis is the smallest unit in the data sample containing information regarding the research question. Graneheim et al discussed that the unit of analysis should be large enough to convey a whole perspective and small enough to be kept in mind as a context for meaning unit during the analysis process [35].

For both case studies, the initial analysis showed that patients' comments were composed of multiple sentences that covered various dimensions and aspects of experiences and concerns. Therefore, we used sentences as the unit of analysis. In addition, data analysis at the level of sentences ensured that no important segment of patient narratives was missed. Splitting patient posts into sentences is not an easy task because of colloquial language and grammatical and punctuation errors. Therefore, we preprocessed the data to remove noisy patterns and then split the patient posts into sentences using open-source Natural Language Toolkit [36]. Multimedia Appendix 4 shows examples of regular expression codes we used to handle the grammatical errors in patient posts.

Phase III: Content Analysis

After preparing the patient posts, the next step is on defining themes for content analysis. The framework method allows different approaches for generating themes: deductive, inductive, and combination of deductive-inductive. In this section, we illustrate the step-by-step procedure of generating themes using deductive-inductive approach for the 2 case studies. This approach allowed us to retest the available knowledge in the literature in the context of patient narratives while leaving space for discovering new aspects of the patient experiences in online health forums.

In this section, we explain the process of generating themes for the case study *attitude to antidepressants*. The process of generating themes for the case study *access to diabetes medications* is presented in Multimedia Appendix 5

Generating Themes Using Deductive Analysis

Our literature review showed that existing knowledge in the literature is useful for generating themes to analyze and summarize patient experiences with antidepressants in online forums. Accordingly, we conducted a systematic literature review to identify significant factors affecting patients' attitudes toward antidepressants. We identified 5 main themes including pharmacological treatment, health care system, social-cognitive and psychological factors, patient-related factors, and depression that influence patients' attitudes toward antidepressants. For each theme, we identified subthemes. Figure 3 shows the themes and subthemes generated using deductive analysis.

To start coding patient posts using the predefined themes, developing guidelines with clear operational definitions for each theme is necessary. Operational definitions should include well-defined statements with explicit inclusion and exclusion criteria describing the segment of a text assigned to a theme. Each statement must accompany 1 or more examples extracted from patient posts. Table 1 provides an example of operational definitions of themes for the case study *attitude to antidepressants*. Multimedia Appendix 6 includes the operational definitions for all predefined themes of the study *attitude to antidepressants*.

Themes generated in deductive approach were used for generating the initial analytical framework. We constructed the framework by organizing predefined themes in the columns and sentences of patient posts (unit of analysis) in the rows. Each patient post was split into sentences and identified using post ID and sentence index indicating the position of the sentence in the patient post. Figure 1 shows the structure of the analytical framework for the case study *attitude to antidepressants.*

Figure 3. Generated themes using deductive approach for the case study attitudes to antidepressants.

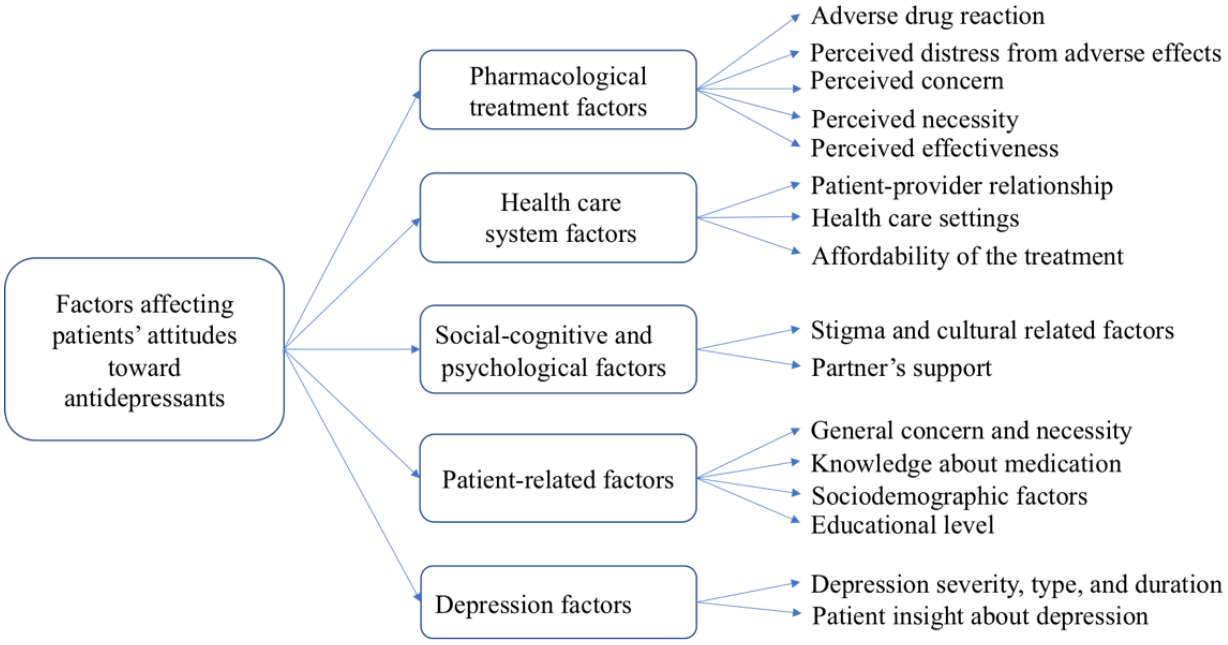


Table 1. Example of operational definition for the themes for the project *patient attitudes toward antidepressants* and category.

Pharmacological treatment factors (predefined codes)	Description
Perceived effectiveness	The patient's subjective assessment of antidepressant helpfulness in the reduction of depression symptoms, enhancing emotional and cognitive functionalities, and overall, enhancing life quality. Example: *Anyway, my life is on track, I have nothing to be depressed or sad about.*
Side effects	Any adverse reactions that the patient reports as adverse reactions to antidepressants intake. Antidepressants' adverse reactions may include physiological side effects, emotional syndromes, cognitive impairment, and limitations on daily functioning and quality of life. Example: *Typical with Effexor XR- Dizzy, jaw tight, teeth grinding.*

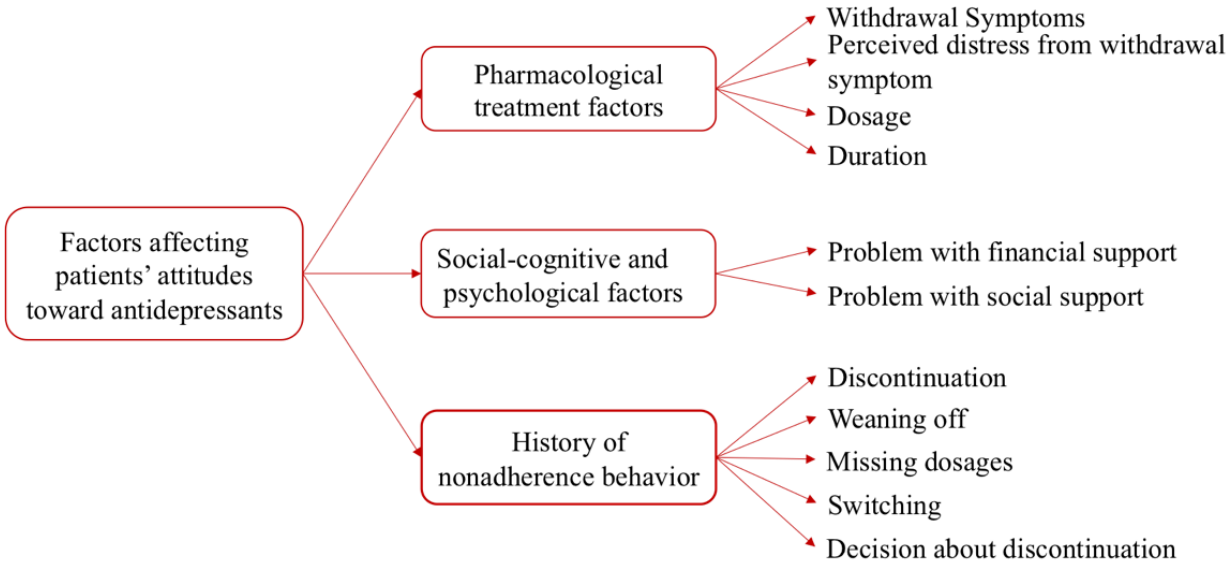
Generating Themes Using Inductive Analysis

As patients in the forums have the freedom to anonymously share their experiences and concerns in the lay language without any limitations, it is likely that patient posts include information that may not fit into the predefined themes in the initial analytical framework. Therefore, in this step, although we coded sentences (of patient posts) using predefined themes, we used the inductive approach to generate new themes for sentences that could not be assigned to the predefined themes.

It is not necessary to use the whole sample for inductive analysis. Researchers may select a random portion of the sample (eg, 30%), regarding the availability of resources, size of a sample, and the level of heterogeneity in patient narratives. For example, in the study *attitude to antidepressants*, we created a subsample by randomly selecting 33.33% (300/900) of the posts for inductive analysis. To identify new themes, 4 coders read the sentences in the subsample and assigned them to proper themes by following the guidelines. The meaningful sentence that could not fit into predefined themes was discussed in our regular team meetings for new themes. For example, we could not assign this sentence *I weaned slowly and I feel nauseous a lot* to any predefined themes to any available themes, so we generated a new theme named *withdrawal symptom*. We created a theme named *Not-applicable* that contained sentences without any meaningful information related to the research question. For example, *Feel free to email me about Effexor* does not reflect any information about the patient's attitude toward antidepressants.

Figure 4 shows new themes generated using the inductive approach for the project attitude to antidepressants. Multimedia Appendix 7 includes all the generated new themes with the examples from patient posts for this study.

Figure 4. Generated themes using inductive approach for the case study "attitude to antidepressants".



Refining the Themes

Some of the themes generated in deductive approach may not fit into patient posts. For example, we could not find any sentences in the subsample of the study *attitude to antidepressants* to assign to the theme *educational level*. In addition, some of the new themes developed through inductive approach may fit into a few patient posts. For example, nearly 1.9% (17/892) of the patient posts in the subsample had information related to *problem with financial support;* therefore, we removed the theme from the list.

Themes generated using inductive and deductive approaches need to be refined before developing the final analytical framework. Theme refining can be conducted by creating rules such as setting a threshold on the number of sentences that should be assigned to a theme. For example, for the study *attitude toward antidepressants*, we set the threshold on 5%, that is, if a theme included less than 5% of sentences in the subsample, we excluded them from the list of themes. The value of the threshold depends on the importance of the rare or uncommon themes (patterns) in the dataset for the research team. For example, for the case study *access to diabetes medications*, we did not consider any threshold because of the importance of the rare information that patients reported to get access to medications. But for the case study *attitude toward antidepressants*, it was not possible to make any conclusion based on the rare themes in the dataset, that is, to measure the association between rare themes and patients' attitudes. Therefore, our research team set the threshold on 5% after the initial analysis of 30% of the dataset.

Multimedia Appendix 8 includes all the rules generated to refine themes for the study *attitude to antidepressants.*

Developing the Guideline for Coding

To maintain consistency and uniformity of coding patient posts using the final themes across the sample, developing guidelines are necessary. Guidelines should include the aim of the project, operational definition of the themes with specific examples from patient posts, and inclusion and exclusion criteria for assigning a unit of analysis to themes. Operational definition for a theme should include a clear and precise statement that enables the annotators to recognize a segment of patient post that fit the theme. For example, theme *adverse drug reaction* (ADR) in the study *attitude to antidepressants* defined as *any signs or symptoms that patients experienced after drug consumption and explicitly and certainly were linked to the drug consumption* includes criteria to decide what is ADR by emphasizing on the time of occurrence of the sign or system, that is, *after drug consumption*. The definition also used the terms *explicitly* and *certainly* to exclude any vague or uncertain statements from the patient post. Vague or ambiguous operational definition increases the need for text interpretation, raises the risk of observational error in coding, and consequently results in low interannotator agreement (IAA).

The guidelines should also include instruction on coding the unit of analysis using themes. For example, whether the unit of analysis can be assigned to more than 1 theme or whether the unit of analysis should be interpreted in the context of the patient posts are important questions. Clear answers to these questions can certainly facilitate the process of coding and increase the quality of generated structured data. Finally, it would be useful if coding guidelines include the list of qualifications for hiring annotators and the estimated time for training. Multimedia Appendix 9 contains the guidelines that we developed for the study *access to diabetes medications.*

Selecting Appropriate Coding Environment

The research team should select a coding environment that facilitates construction of the analytical framework and the process of coding. For both case studies explained in this study, we used a spreadsheet to construct the analytical framework (see Figure 1). Annotators (coders) could assign a sentence to a theme by inserting 1 in the intersection of the sentence and the theme. However, if the unit of analysis is a phrase or a word, the spreadsheet may not be a convenient tool for constructing the analytical framework and annotating process. In this case,

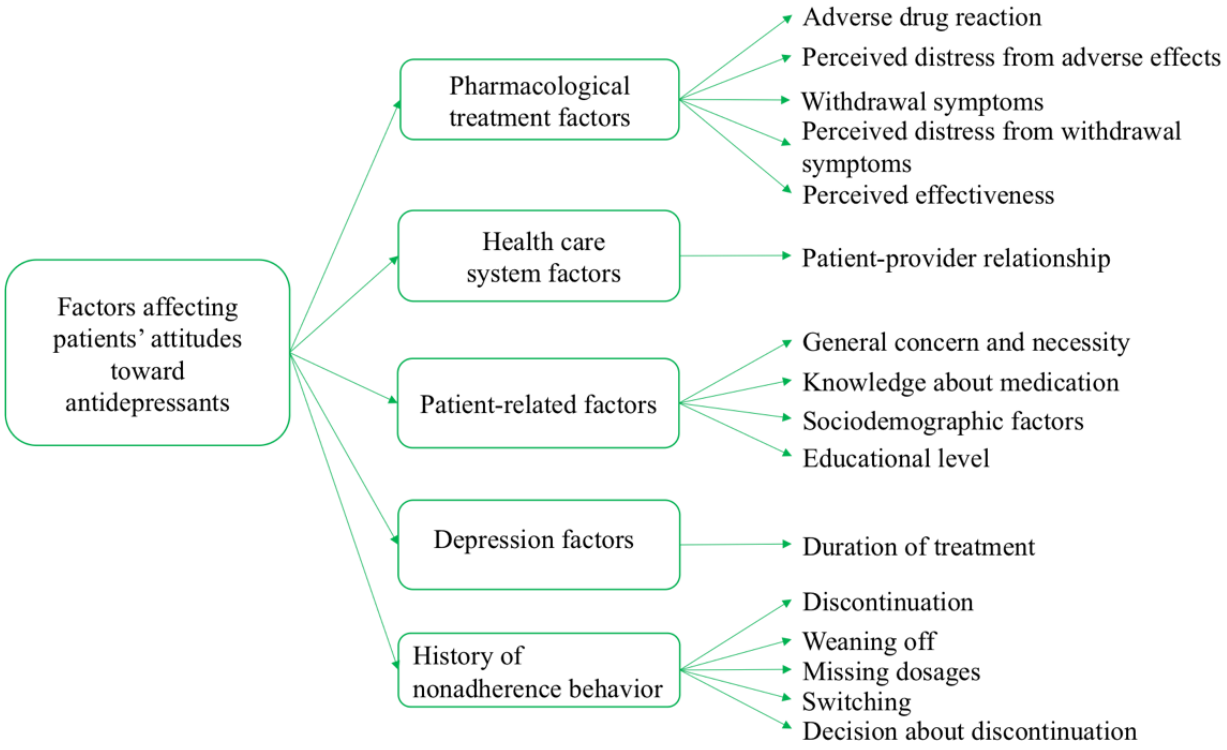
tools such as *Brat* [37] or *MAE* [38] are helpful. But if the unit of analysis can be defined as any segment of text (patient post), tools that were specifically designed for qualitative data analysis, such as NVivo (a qualitative data analysis (QDA) computer software package produced by QSR International) [39], would be more useful.

Developing the Final Analytical Framework

Overall, the final themes should meet the following criteria: (1) valid—themes should accurately reflect what is being measured, (2) mutually exclusive—themes should not overlap between operational definitions, and (3) exhaustive—themes should cover all the aspects of the data related to the research question. *All* aspect of the data means identifying all the dimensions of the dataset that provide meaningful information for the research question.

Figure 5 shows the final themes after refining them for the study *attitude toward antidepressants*. The refined themes were used for constructing the final analytical framework. Multimedia Appendix 10 presents the final analytical framework with all the themes and examples from patients' drug reviews.

Figure 5. Final themes for the case study "attitude to antidepressants".



Phase IV: Analysis of Findings

Before researchers summarize and interpret the data, they should evaluate the quality of the produced structured data. As assigning a certain observation of patient narratives to themes is a subjective process, a disagreement may happen between annotators (coders). In this section, we explain measures for computing IAA and then discuss summarizing and interpretation of the findings.

Computing Interannotator Agreement

Cohen kappa is the most popular method for computing IAA. It measures the agreement between 2 annotators who annotate N items (eg, 100 sentences) into M mutually exclusive themes (eg, 10 themes) and corrects the result for the agreement that would be expected by chance [40,41]. Possible values for the kappa coefficient ranges from –1 to 1, where 1 indicates complete agreement, 0 indicates completely random agreement, and –1 indicates complete disagreement. For the formula of Cohen kappa and detailed interpretation on the obtained values, see Multimedia Appendix 11 [42,43].

To improve the quality of produced structured data, researchers may decide to annotate each document (eg, patient post) by more than 2 annotators. In this case, Fleiss kappa (an adaptation of Cohen kappa for 3 or more raters) should be used for computing the IAA [41].

There are other methods for calculating IAA, such as pairwise agreement. If the annotation task requires identifying terms or phrases and determining their correct boundaries (eg, identifying sign or a symptom) in the patient's posts, the pairwise agreement would be an appropriate measure. The kappa coefficient would not be suitable because the chance agreement is effectively 0 in this case. Please see Zolnoori et al [7] for the formula and examples related to computing pairwise agreement.

Interpretation of Findings

If the structured data developed during the process of content analysis is rich enough, it can provide substantial insight into patients' concerns, needs, preferences, and attitudes. Interpretation of the result could start with a general description of the themes, followed by reporting the most frequent and infrequent identified patterns, and finally reporting the unexpected patterns in data. Multimedia Appendix 12 provides a descriptive interpretation of the findings of the case study *access to diabetes medications.*

Implication of Findings

The findings of content analysis can go beyond a simple description of themes. In fact, it can be used for describing patterns or regularities, generating and testing hypotheses, describing a phenomenon and the associated factors, identifying problematic areas in the health care systems, or even developing predictive models to predict a specific patient's behavior, such as medication nonadherence behavior. For example, for the project *attitude to antidepressants*, we tested the association between themes (variables) and patient attitudes toward antidepressants using statistical methods (analysis of variance and chi-square test) [11].

Discussion

Efficient Qualitative Research

Qualitative content analysis approaches are nonlinear, and iterative processes are more complicated than quantitative approaches because they are less structured and standardized. There are no single guidelines for content analysis. Selecting a specific approach strongly depends on the aim of the study, the research question, and the type of qualitative data. Researchers collecting and analyzing qualitative data, such as patient narratives, often wish to have a systematic approach including the detailed instruction on how to conduct qualitative research efficiently.

This study provided a systematic framework for the content analysis of patient-generated narratives in online health forums (communities). The systematic framework was built on text mining approaches for data collection and data preprocessing and qualitative content analysis using the framework method with the deductive-inductive approach for themes generation. We showed the feasibility and usefulness of the proposed systematic framework using 2 case studies: (1) a published study with a focus on identifying factors affecting patients' attitudes toward antidepressants [11] and (2) an ongoing study with the focus on strategies and solutions of patients with diabetes facing financial difficulties to access medications and supplies. The data sources for these 2 studies were from online health forums. Using the systematic framework specified in this study, we could generate high-quality structured data that not only could identify the different dimensions and aspects of patients' experiences but also could be used for testing hypotheses concerning the relationships between variables (themes) [11]. In addition, the structured data could also be used to train text mining algorithms to identify specific health-related information from patients' narrative data [7].

The core component of the proposed framework (phase 3) is the framework method for qualitative content analysis [10]. Its prominent feature is the facilitation of *constant comparative method* through a matrix structure of the data. The matrix structure provides an intuitively structured overview of the summarized data that can facilitate and accelerate the identification of patterns and themes by highlighting the contradictory data and irregular cases. More importantly, it keeps a clear map between original data and themes in the analytical framework, indicating illustrative quotes for themes.

We used a combination of deductive-inductive approach to develop themes for both case studies in this study. However, the proposed systematic framework can be applied equally to studies aimed to use only inductive or deductive approach for data analysis. Our literature review showed that studies with focus on the qualitative content analysis of patient narratives in online health forums mostly used inductive approach for theme generation. But, we showed that the deductive analysis could accelerate the inductive analysis of patient narratives and identify new patterns and themes. There are major differences between this systematic framework proposed in this study and the framework of content analysis suggested by other papers. Please see Multimedia Appendix 13 for this difference [44,45].

Limitations

We acknowledge some limitations with our proposed framework:

1. It is not appropriate for the analysis of very heterogeneous patients' narratives, for example, if the patients' experiences and the discussions in health forums are very diverse and cover a wide range of health topics. The systematic framework is most suitable for the studies with research questions targeting specific patient cohort with shared health concerns and experiences (eg, medications' effects or difficulty in access to a health services).
2. It is not suitable for qualitative studies aiming at developing a theory or analysis of the structure of the experiences or language or the social context associated with the language. The research team may adopt other qualitative approaches to achieve the aims, such as approaches for developing theories derived from the data (eg, grounded theory) [46], approaches with focus on identifying the structure of an individual's experience (eg, phenomenology) [47], approaches with concern about the relationship between language and the social structure in which the language is used (eg, discourse analysis and ethnomethodology) [48], and approaches designed with the aim of investigating intention and language (eg, narrative analysis) [49].
3. Although it provides a detailed instruction on analysis of patient posts, which may save time and resources similar to other qualitative analysis methods, it is still time consuming and resource intensive when involving time needed for developing guidelines and training annotators. This time needs to be factored into the study methods and approach.

Lessons Learned

Previous experiences with and lessons learned from the content analysis:

- Qualitative content analysis may seem confusing and complicated for novice researchers. They may find this process to be chaotic and grapple with the qualitative research terms and concepts, such as patterns, categories, and themes. But experiencing chaos during the analysis is normal. Qualitative researchers need to be open to the complexity of content analysis [50] and improve their experience for systematic thinking.
- During the content analysis process, it would be very helpful to review the research questions constantly. Frequently referring to the research question and aim of the study will help researchers to stay focused on only dimensions of the dataset that answer the research question. It is also very important to take a note of new ideas and identified themes during the whole process of analysis. If the data analysis is conducted in an Excel sheet, assigning a column to notes and ideas would be very useful.
- Content analysis is a very time-consuming process and unexpectedly challenging [12]. The research team should plan ahead to have sufficient time to think, reflect, and then conduct a review of the analysis.
- It is important to avoid any preunderstanding of the dataset to minimize the risk of bias during the process of content analysis and interpretation of the results [9].
- It is important to have a weekly meeting to discuss new ideas and identified patterns in the group. All team members should be open and receptive to new ideas. The research team should proceed with defining and updating analytical framework based on the summary of the meeting discussion each week.
- Creating a table or figure containing information about the process of analysis from the raw data to a meaningful unit of analysis, to the identified themes with examples from patients' post would be very useful. Including the figure or table in the manuscript of the study will show the validity of the study and improve appreciation of reviewers and readers of the study's findings.

Conclusions

Exploring patient-reported experiences and concerns in online health care forums (communities) and translating such content into meaningful concepts (themes) has become a challenge for health care researchers and health care providers. In this study, we introduced a systematic framework as a rigorous and standardized method to collect patient-reported experiences from online forums and convert their content to themes that are reliable and easily interpretable. The framework was built on the text mining approaches and the framework method with the deductive-inductive approach that benefit both researchers and clinicians by minimizing the cost, time, and human errors during the process of data processing and analysis. We showed the reliability and efficiency of this framework using 2 case studies: one identifying factors associated with patients' attitude toward antidepressants and the other identifying solutions and strategies of patients with diabetes facing financial difficulties to access medications and supplies. Finding meaningful information through such a process indicates authentic dimensions and aspects of patient experiences and sheds light on patients' concerns, needs, preferences, and values, which are the core of patient-centered care.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Definition of HTML, API, Web crawler, Python package, and XML.
[PDF File (Adobe PDF File), 64KB - resprot_v8i8e13914_app1.pdf]

Multimedia Appendix 2
Kinship terminology and UMLS (Unified Medical Language System).
[PDF File (Adobe PDF File), 47KB - resprot_v8i8e13914_app2.pdf]

Multimedia Appendix 3
Example of a formula for determining the sample size.
[PDF File (Adobe PDF File), 111KB - resprot_v8i8e13914_app3.pdf]

Multimedia Appendix 4
Examples of regular expression codes for reducing noise patterns in patients' posts.

[PDF File (Adobe PDF File), 183KB - resprot_v8i8e13914_app4.pdf]

Multimedia Appendix 5
Case study #2: strategies and solution of diabetes patients with financial difficulties for accessing medications and supplies.
[PDF File (Adobe PDF File), 373KB - resprot_v8i8e13914_app5.pdf]

Multimedia Appendix 6
Operational definitions for all predefined themes for the case study “identifying factors affecting patients’ attitudes towards antidepressants”.
[PDF File (Adobe PDF File), 148KB - resprot_v8i8e13914_app6.pdf]

Multimedia Appendix 7
New themes generated through inductive approach for the case study “identifying factors affecting patients’ attitudes towards antidepressants”.
[PDF File (Adobe PDF File), 107KB - resprot_v8i8e13914_app7.pdf]

Multimedia Appendix 8
Rules for refining the identified themes.
[PDF File (Adobe PDF File), 154KB - resprot_v8i8e13914_app8.pdf]

Multimedia Appendix 9
Guidelines for annotating the patients comments for the case study “diabetes patients solutions to access medications and supplies in the context of financial difficulties”.
[PDF File (Adobe PDF File), 179KB - resprot_v8i8e13914_app9.pdf]

Multimedia Appendix 10
Final analytical framework for the case study “identifying the underlying factors affecting patient attitudes toward antidepressants”.
[PDF File (Adobe PDF File), 228KB - resprot_v8i8e13914_app10.pdf]

Multimedia Appendix 11
Interpretation of the obtained results from the Cohen kappa.
[PDF File (Adobe PDF File), 89KB - resprot_v8i8e13914_app11.pdf]

Multimedia Appendix 12
Descriptive interpretation of the findings of the case study “access to diabetes medications”.
[PDF File (Adobe PDF File), 85KB - resprot_v8i8e13914_app12.pdf]

Multimedia Appendix 13
The major difference between the systematic framework and other content analysis frameworks.
[PDF File (Adobe PDF File), 61KB - resprot_v8i8e13914_app13.pdf]

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Abbreviations

ADR: adverse drug reaction
API: application programming interface
IAA: interannotator agreement
IRB: institutional review board
NLP: natural language processing
UMLS: Unified Medical Language System

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Protocol

Evaluation of a Collaborative Protocolized Approach by Community Pharmacists and General Medical Practitioners for an Australian Minor Ailments Scheme: Protocol for a Cluster Randomized Controlled Trial

Sarah Dineen-Griffin[1], BBSc, Grad Cert (Pharmacy Practice), MPharm; Victoria Garcia-Cardenas[1], BPharm, PhD; Kris Rogers[1], MBioStats, PhD; Kylie Williams[1], BPharm, PhD; Shalom Isaac Benrimoj[2], BPharm (Hons), PhD

[1]Graduate School of Health, University of Technology Sydney, Ultimo, Australia

[2]Emeritus Professor, The University of Sydney, Camperdown, Australia

Corresponding Author:
Sarah Dineen-Griffin, BBSc, Grad Cert (Pharmacy Practice), MPharm
Graduate School of Health
University of Technology Sydney
15 Broadway
Ultimo, 2007
Australia
Phone: 61 (02) 9514 7677
Email: sarah.dineen-griffin@uts.edu.au

Abstract

Background: Internationally, governments have been investing in supporting pharmacists to take on an expanded role to support self-care for health system efficiency. There is consistent evidence that minor ailment schemes (MASs) promote efficiencies within the health care system. The cost savings and health outcomes demonstrated in the United Kingdom and Canada open up new opportunities for pharmacists to effect sustainable changes through MAS delivery in Australia.

Objective: This trial aims to evaluate the clinical, economic, and humanistic impact of an Australian Minor Ailments Service (AMAS) compared with usual pharmacy care in a cluster randomized controlled trial (cRCT) in Western Sydney, Australia.

Methods: The cRCT design has an intervention group and a control group, comparing individuals receiving a structured intervention (AMAS) with those receiving usual care for specific health ailments. Participants will be community pharmacies, general practices, and patients located in Western Sydney Primary Health Network (WSPHN) region. A total of 30 community pharmacies will be randomly assigned to either intervention or control group. Each will recruit 24 patients, aged 18 years or older, presenting to the pharmacy in person with a symptom-based or product-based request for one of the following ailments: reflux, cough, common cold, headache (tension or migraine), primary dysmenorrhea, or low back pain. Intervention pharmacists will deliver protocolized care to patients using clinical treatment pathways with agreed referral points and collaborative systems boosting clinician-pharmacist communication. Patients recruited in control pharmacies will receive usual care. The coprimary outcomes are rates of appropriate recommendation of nonprescription medicines and rates of appropriate medical referral. Secondary outcomes include self-reported symptom resolution, health services resource utilization, and EuroQoL Visual Analogue Scale. Differences in primary outcomes between groups will be analyzed at the individual patient level accounting for correlation within clusters with generalized estimating equations. The economic impact of the model will be evaluated by cost-utility and cost-effectiveness analysis compared with usual care.

Results: The study began in July 2018. Thirty community pharmacies were recruited. Pharmacists from the 15 intervention pharmacies were trained. A total of 27 general practices consented. Pharmacy patient recruitment began in August 2018 and was completed on March 31, 2019.

Conclusions: This study may demonstrate the efficacy of a protocolized intervention to manage minor ailments in the community and will assess the clinical, economic, and humanistic impact of this intervention in Australian pharmacy practice. Pharmacists supporting patient self-care and appropriate self-medication may contribute to greater efficiency of health care resources and integration of self-care in the health system. The proposed model and developed educational content may form the basis of a national MAS service in Australia, using a robust framework for management and referral for common ailments.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12618000286246; http://www.anzctr.org.au/ACTRN12618000286246.aspx

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KEYWORDS

pharmacy; pharmacists; general practitioners; primary health care; community pharmacy services; nonprescription drugs; self care; self medication; randomized controlled trial; Australia

Introduction

Integrated care is a possible solution to the rising demand in facilitating appropriate delivery of health services and limiting fragmentation between health care providers. Evidence indicates that health systems with strong integrated primary health care are effective in improving patient outcomes and efficient at delivering high-quality appropriate services [1,2]. Many countries have undergone major health reforms to deliver effective and efficient health care, moving toward sustainable health systems that are both durable and resilient to withstand impending and ongoing challenges [3-6]. As an example, the Australian health system has undertaken significant reform and restructuring to improve value for investment in health care [2,7] through the establishment of Primary Health Networks (PHNs). Their objectives are delineated as (1) delivering health care services that increase the efficiency and effectiveness for patients and (2) strengthening the degree of coordination and connectivity of care, ensuring patients receive the right care, in the right place, at the right time [8].

Major questions exist surrounding how health care systems can address minor ailments more efficiently through the use of administering care in less expensive settings such as community pharmacy [9,10]. Minor ailments have been defined as "conditions that are often self-limiting, with symptoms easily recognized and described by the patient and falling within the scope of pharmacist's knowledge and training to treat" [11]. It is already known that patients self-manage conditions to a large extent [12], and encouraging people to exercise greater levels of self-care, either for acute or chronic problems, has significant potential to directly affect demand for, and shift costs from, medical health care. Pharmacists are positioned to facilitate self-care and appropriate self-medication processes [13]. Undoubtedly, the expansion of nonprescription medicines has given patients greater choice, providing community pharmacy with an opportunity to demonstrate real and tangible benefits by facilitating this process [13]. Community pharmacy has been transforming to a service provider model driven primarily by leadership of professional organizations, government policies, remuneration, and patient needs. The community pharmacy sector has undergone changes such as enhancing the pharmacists' role in providing professional pharmacy services to optimize the process of care [14]. Community pharmacy provides a range of remunerated commissioned and noncommissioned professional pharmacy services that have shown to be cost-effective compared with other health care settings and contribute to improved health outcomes for patients [15-18]. Importantly, pharmacists can be better integrated within primary care. Effective collaboration between general medical teams and community pharmacies will be integral to achieve the highest level of patient care [8,19].

There is consistent evidence at an international level that pharmacy-based minor ailment schemes (MASs) promote efficiencies of use within the health care system [20]. MASs were introduced for patients to access professional support for conditions that can be self-managed with the objectives of increasing accessibility, providing the right level of care and mitigate funding and system inefficiencies [21]. A total of 94 international schemes are identified in the literature across 103 regions, including the United Kingdom (England, Scotland, Northern Ireland, and Wales) [20,22-26]. Minor ailment assessment and prescribing is the nomenclature used in Canada, representing a pharmacy service that allows pharmacists to prescribe certain drug groups for the treatment of minor, self-diagnosed, and/or self-limiting conditions. Of 13 provinces in Canada, 8 operate a Minor Ailments Prescribing Service [27-28]. Each of these services is slightly unique in its feature and structural design parameters [20]. MASs have been included in the policy agenda in Australia [29-31] and New Zealand [32]. Paudyal et al explored the effect of MAS on patient health and cost-related outcomes [21]. The review showed low reconsultation and high symptom resolution rates of up to 94% with MAS, suggesting minor ailments are being dealt with appropriately in pharmacy [21]. The positive economic impact has shown international MAS to be cost-effective compared with more expensive health care services, such as general practice and accident and emergency (A&E) departments [16]. There are different models of general practitioner (GP)-pharmacist collaboration offering the community pharmacy network to be better integrated into general practice or urgent and emergency care systems. One example in the United Kingdom is the provision of integrated out-of-hours services by community pharmacy, such as the Digital Minor Illness Referral Service [12]. The service evaluates the way in which patients with self-limiting minor ailments who are contacting urgent services can be supported by community pharmacists instead of being booked for an urgent GP appointment or signposted to their own GP.

Pharmacists treating patient's common ailments, the exclusive availability of nonprescription products through pharmacies to provide symptomatic relief, and referral to other health care professionals is a well-established activity within pharmacy practice. Unfortunately, in Australia, there is limited standardization and protocolization for consultations and procedures for escalating referral. There is minimal integration with general practice systems and no formal method of

physician-pharmacist collaboration or communication relating to minor ailments, and the nature and extent of collaboration may be seen as both episodic and informal. This invariably limits facilitated self-medication practices. In addition, there are no mechanisms to monitor or document patient interactions, resulting in missed opportunities to identify patients who require referral, limiting the ability to detect inappropriate or continued use of nonprescription medicines. The potential for community pharmacists to moderate patients' needs for the treatment and management of minor ailments and alleviate health system pressure in Australia has been recognized [33,34].

The Australian Minor Ailments Service (AMAS) is a practice model with key elements, such as agreed referral points, communication systems between pharmacists and general practitioners (GPs), and clinical treatment pathways, that is, *HealthPathways*. The conceptualized components of AMAS have been developed in consultation with key stakeholders including PHN leaders and, importantly, leading general medical professionals involved in PHN governance in Australia. Input into design and agreement with stakeholders have progressed the development of collaborative referral pathways, providing a robust framework for community pharmacists to deliver evidence-based minor ailment care. In essence, these pathways seek to improve the coordination and delineation of health care provider roles for minor ailments with sequencing of care through referral that is agreed between pharmacists and general practice for health system efficacy and optimal quality [1,12,35-39]. Specifically, assurance of quality in health service provision may be achieved through the evaluation of standardized condition management and differential diagnosis tools such as *HealthPathways* [40], robust referral processes for escalation, and service delivery by the pharmacist themselves.

In achieving the stated objectives, we may provide evidence that a scheme would be successful in Australia. Community pharmacists offering an enhanced self-care model can make a significant contribution to Australian health care and reduce the substantial burden on other primary care providers with pharmacists providing the appropriate level of care for minor ailments and checking on patients who are self-medicating. The integration of community pharmacists into primary health care would better enable primary care to be delivered in a structured manner. In addition, the systematization of clinical decision making and referrals through relatively easy-to-update protocols would improve service navigation and the patient journey. The development of new clinical pathways in the area of minor ailments seeks to standardize practice according to the best available evidence and reduce variations in current practice. Increased interprofessional teamwork and collaboration between GPs and community pharmacists for care coordination would increase the likelihood of reaching treatment goals and improving patient outcomes. Community pharmacists will gain from having evidence-based guidance, and the community will benefit from another mechanism to ensure that advice from a pharmacist is based on the latest available evidence. AMAS facilitates increased access to care for individuals to receive minor ailment treatment in a timely and efficient manner.

This paper describes a research protocol to evaluate a collaborative protocolized AMAS to improve the management of common ailments in Australia. The AMAS intervention outlined in this study protocol offers a unique and innovative approach to address self-medication and formalize triage processes in the Australian primary care system. The principal aim of this study is to evaluate the clinical, economic, and humanistic impact of AMAS on adult patients attending Australian community pharmacies compared with usual pharmacist care.

Methods

Study Design and Setting

The study will use a community pharmacy-based cluster randomized controlled trial (cRCT) design with an intervention group and a control group following the Standard Protocol Items: Recommendations for Interventional Trials checklist [41] (Multimedia Appendix 1). The study will be performed over 8 months in community pharmacies throughout Western Sydney Primary Health Network (WSPHN) region.

Recruitment of Study Participants

Participant recruitment will occur at 3 levels: community pharmacy, general practice, and patient level.

Pharmacy Level

Community pharmacies located in WSPHN region with a pharmacist available to attend specialized training to deliver the AMAS service will be eligible to participate in the study. Contact information of pharmacies will be retrieved from publicly available lists, and those meeting criteria for inclusion will be invited to join the study by telephone. The lead researcher will arrange face-to-face discussion for those expressing interest and to obtain written consent for participation. Randomization will be at the level of the community pharmacy. Pharmacies will be sequentially numbered according to their order of acceptance into the study. An independent researcher will assign the pharmacies (units of randomization) to either the intervention group or control group based on unrestricted random sampling using a computer-generated random number list with a ratio of 1:1 in Excel 2016 (Microsoft Corporation).

General Practice Level

Representatives from WSPHN will assist in the engagement and recruitment of general practices within WSPHN into the study. An expression of interest will be forwarded by a blast email to all practices located within the region. The WSPHN representative will provide follow-up information for those expressing interest, and consent will be sought at the practice level from GP practice managers overseeing the work of the surgery or group of surgeries. Each practice manager will be requested to ensure individual GPs within the consented practice are made fully aware of their role within the study before commencement. Study information will be circulated to individual practitioners detailing GP involvement, and given the option of contacting the research team with further questions. Signed practice consent forms will be forwarded to the lead

researcher. Informed consent will be essential to receive information from the pharmacist. The details of individual GP involvement in the study are provided below.

Patient Level

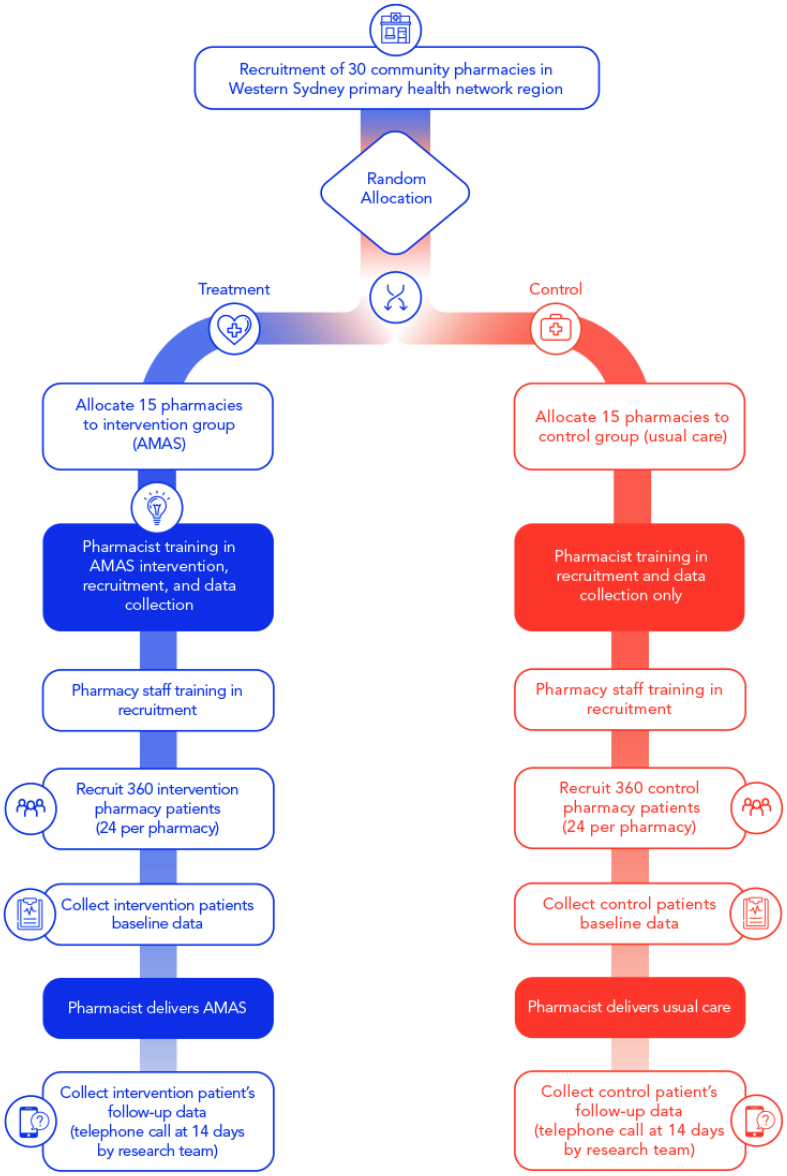
Patients will be recruited from participating pharmacies. Consecutive recruitment will be used. The recipients of the AMAS service or usual care will be patients who request management for their minor ailment symptoms (symptom-based request) and/or self-select a product to self-treat their ailment (product-based request). The patient may either initiate an interaction or wait to be approached by a member of pharmacy staff while self-selecting a product. The pharmacy team member will refer the patient to the pharmacist who will offer participation in the study if eligible to participate. Patients aged 18 years or older will be identified as eligible if meeting all the qualifying criteria, including (1) attending the pharmacy in person, (2) presenting with a symptom-based and/or product-based request for one of the included minor ailment conditions from 3 specific symptom groups (Table 1), (3) ability to provide written informed consent to participate in the study, and (4) accessible by telephone.

Eligible patients identified by the pharmacist will be provided a Participant Information and Consent Form (PICF) explaining the study and given the opportunity to ask questions. Further discussion will be conducted at a private area in the pharmacy or an area appropriate for the discussion to be performed in a confidential manner. Those agreeing to participate will be asked by the pharmacist to provide signed consent. On the basis of which pharmacy they attend, patients will receive the intervention or usual care (Figure 1).

Table 1. Minor ailment conditions.

Classification	Minor ailments to be included in the study
Gastrointestinal	Reflux or indigestion
Respiratory	Cough and common cold
Pain	Headache (tension or migraine), primary dysmenorrhea (period pain), and low back pain

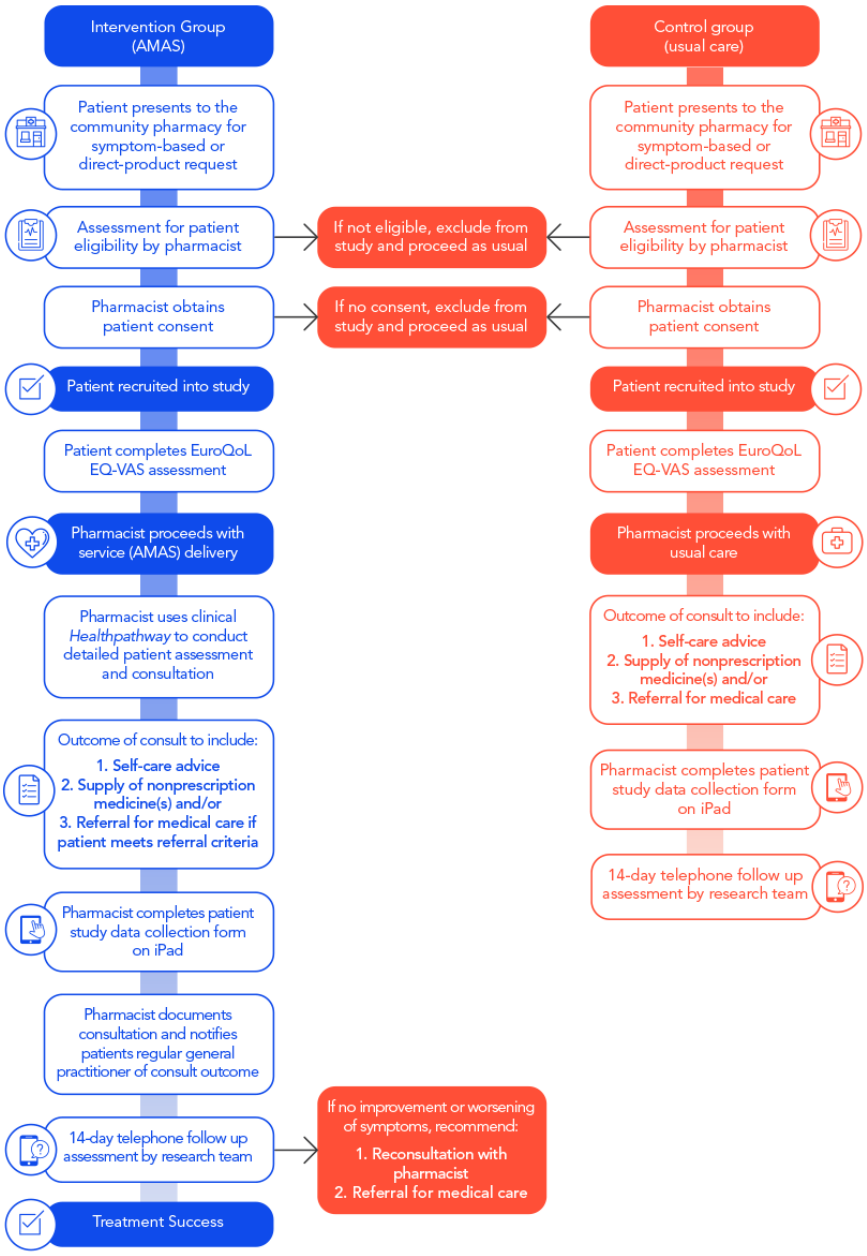
Figure 1. Study design. AMAS: Australian Minor Ailments Service.



Description of Intervention

As we are aiming to evaluate the impact of an enhanced service compared with the one that is already being delivered in routine practice, intervention patients will receive AMAS on presentation to the pharmacy. This will involve a protocolized face-to-face pharmacist-patient consultation. Pharmacists will follow a number of steps in the patient encounter (Figure 2). Patients will be followed up at 14 days after the initial patient-pharmacist consultation through telephone by the research team to assess for resolution of symptoms and health care utilization for the same ailment.

Figure 2. Usual care versus intervention: clinical management algorithm. AMAS: Australian Minor Ailments Service; EQ-VAS: EuroQoL Visual Analogue Scale.



We are proposing a number of innovative features to AMAS, which are described below.

Collaborative Treatment Pathways for Minor Ailments

Clinical pathways are "document-based tools that provide recommendations, processes, and time frames for the management of specific medical conditions or interventions" [42]. They define a process of care agreed by local clinicians and pharmacists and are informed by existing evidence, guidelines, and protocols. *HealthPathways* is a proprietary system of clinical pathways developed in New Zealand and adopted by clinicians throughout PHNs in Australia [40]. These pathways seek to serve as guidance for desired standards of practice and are ultimately intended to promote consistency and uniformity of care.

The collaborative clinical pathways for each minor ailment (Table 1) are intended for use by community pharmacists delivering AMAS. Each ailment has the same structure and format to make the process of finding and using the information easy and practical. These pathways include types of questions, assessment, management approach recommending a particular course of action including self-care, and/or a nonprescription medicine for symptomatic relief, specific to each ailment. Included is a robust framework for referral, indicating red flag criteria to trigger escalation processes, and the time frame within which a patient is recommended to seek care from a particular health care provider (ie, the patient is recommended to see a GP within 24 hours). A red flag is a symptom that is recognized as likely to be of a more serious nature and requires immediate referral. The research and writing of these clinical pathways followed a literature review of contemporary international and

national clinical guidelines in consultation with leading general medical professionals involved in PHN governance with comprehensive experience in *HealthPathways* development.

Pharmacist-Directed Care and Data Collection

Pharmacists will undertake a consultation with eligible patients for symptom-based and product-based requests in the community pharmacy. Intervention pharmacists will use the agreed clinical pathways to recommend a particular course of action, including self-care and/or nonprescription medicine recommendation for symptomatic relief and/or referral. In case of the need to refer, the pharmacist will appropriately escalate if the patient meets criteria for referral for further assessment and/or prescribing of prescription-only medicine.

Collaborative Approach to Management, Follow-Up, and Data Collection

The *HealthLink* system is used by clinicians in Australia [43]. This system allows for the encrypted transmission of clinical and patient confidential information securely and reliably between GPs and community pharmacists. For AMAS patients who have identified a regular GP during the patient-pharmacist consultation, the consultation will be documented and forwarded from the pharmacist to the GP, outlining clinical assessment undertaken, observations, presentation, and consult outcomes (ie, medication supply, pharmacist-directed self-care, and/or details of referral). Details of the consultation will not be provided if (1) the patient has not consented, (2) the patient has not identified a regular GP, (3) the practice has not consented to partake in the study, or (4) the practice is not using HealthLink software. Importantly, the use of this communication system has been agreed with local clinicians within WSPHN. The process of rolling out this system to pharmacies, set up, and licensing will be facilitated by the PHN and project team. If a patient's identified GP has not consented to the study or does not use this software in practice, the pharmacist will still provide the AMAS service (ie, following management pathways and referral if required), yet GPs will not receive feedback on details of their patient's consultation.

Training Pharmacists to Deliver Australian Minor Ailments Service

Intervention pharmacists will attend one of two 7.5-hour training workshops at WSPHN before delivery of AMAS. The aim of educational training is to ensure pharmacists competency in delivering the service. The 2016 National Competency Standards Framework for Pharmacists in Australia [44] and the Pharmaceutical Society of Australia's Professional Practice Standards (version 5) [15] informed the development of content emphasizing competencies to enhance the pharmacist's role in service provision. The training program will also be a refresher about current best practice in common ailments. The workshop will include a combination of lecture presentations and interactive sessions including role-play scenarios. Self-care information and resources for consumers, clinical treatment pathways, communication and data collection software are available on provided iPads to be used at the point of care. Given that pharmacy assistants are likely to be the very first point of contact in the pharmacy, a researcher will visit each intervention pharmacy to train pharmacy assistants in recruitment and will be given the opportunity to ask questions. During this visit, training materials will be revisited with a *champion* pharmacist who will have attended one of the training days before commencing recruitment.

Practice Change Facilitation to Support Intervention Pharmacies

Practice change facilitators (PCFs) will visit intervention pharmacies at least monthly to support the delivery of AMAS. The PCF will be involved in a range of change facilitation processes and activities during visits with the objective of ensuring recruitment targets are met, quality of service provision, quality of data entry, and adherence to the intervention protocol. PCFs will be trained to ensure these objectives are met. These include addressing any barriers to change using evidence-based strategies. PCFs will be collecting both quantitative and qualitative data on-site. This role works closely with the research team.

Control Group

Pharmacies randomized to the usual care arm will receive training in the use of data collection materials and recruitment only. One training night (2 hours) in data collection and recruitment will be provided at WSPHN. A researcher will visit each of the 15 control pharmacies to deliver study materials, and pharmacists unable to attend the training night will be trained in-store. Materials to be provided include study information detailed in the PICF, data collection software for use on provided iPads, and detailed instructions for data collection. Training will be provided to pharmacy staff to support recruitment for the pharmacist. Patient recruitment will begin immediately after this visit. The pharmacist will check patient eligibility, obtain informed consent, and will document control patients' baseline data and proceed with usual care using their own clinical judgment, processes, and resources. Patients will be followed up at 14 days after the initial patient-pharmacist consultation by the research team to assess for resolution of symptoms and health care utilization.

Data Collection Methods

Data will be collected at 2 time points in both intervention and control arms—baseline and 14 days after the consultation. All patients will complete a baseline questionnaire in the pharmacy, including demographic characteristics, and EuroQoL Visual Analogue Scale. Additional data about patient's ailment history, their contact details, and pharmacist intervention will be collected by pharmacists using forms on iPads provided for that purpose. The time taken per patient to deliver the intervention or usual care will be recorded to inform the economic analysis. Follow-up telephone questionnaires will be conducted by research assistants using forms provided for that purpose. Follow-up at 14-days is considered appropriate because of the nature and duration of minor health symptoms. Study data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Technology Sydney (UTS) [45]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an interface for validated data entry, (2) audit trails for

tracking data manipulation and export procedures, (3) automated export procedures for data downloads to statistical packages, and (4) procedures for importing data from external sources [45]. All data collected in pharmacies will be returned to the research team on the day of recruitment to allow for timely follow-up. The chief investigator will have access to the trial data.

Study Measurements and Outcomes

The evaluation of MAS compared with usual care will be achieved by comparing the primary and secondary outcomes [46] as set out in Multimedia Appendix 2.

Sample Size

The primary joint outcome measures of the study are appropriate medical referral rate and appropriate recommendation of nonprescription medicines. Sample size calculation was based on an assumed baseline appropriate medical referral rate of 85% and assumed baseline appropriate recommendation of nonprescription medicines rate of 82% [47,48]. Pharmacies are the primary unit of randomization with individual patients nested within pharmacies. The rate of the joint outcomes will be compared between the treatment and control arms in the study. To test for a 10% absolute increase in primary outcomes (appropriate medical referral rate: 85%-95% and appropriate recommendation of nonprescription products 82%-92%) with ≥0.9 power, alpha of .05, equal allocation ratio, and assuming intracluster correlation is 0.01, we would need 30 pharmacies (15 in each arm) with 24 participants per pharmacy (allowing for 10% dropout) for an overall sample of 720 patients.

Blinding

Given the cluster design, it will not be possible for participating pharmacies to be blinded to group assignment. However, the patient, research assistants conducting follow-up, and the data analyst will be blinded to treatment assignment.

Postrecruitment Retention Strategies

All recruited pharmacies will be contacted by telephone in the first 2 weeks of commencing patient recruitment to address any teething issues with study procedures. Support to resolve any problems will be offered by PCFs (for intervention) or a study researcher (for control). Intervention fidelity will also be monitored by PCFs. Regular newsletters and emails will be sent to all pharmacies during the study period for encouragement, provision of feedback surrounding data quality, and strategies to enhance recruitment to meet desired targets. Pharmacies not meeting target recruitment will be offered additional in-pharmacy support by the study researcher. Recruited patients will be contacted by telephone. Attempts to contact nonresponders will continue until contact is made or for a maximum of either 1 week or 5 call attempts.

Statistical Methods and Analysis

Data will be analyzed using Stata 16 for Windows [49]. Baseline pharmacy and patient level information will be summarized by treatment arm. Continuous variables will be summarized with mean and standard deviation with median and interquartile range provided if the data are skewed. Categorical variables will be summarized by frequency and proportion. Generalized estimating equations will be used to account for within-cluster correlation [50] using an exchangeable correlation structure. A modified Poisson regression approach will be used for the analysis to estimate relative rates (RRs) [51,52]. If the estimation of RR is not computationally achievable, we will estimate odds ratios with logistic regression [50]. As a secondary analysis, we will adjust for key baseline covariates at both the pharmacy level (eg, pharmacy type) and the patient level (eg, age and sex). We plan to conduct an exploratory subgroup analysis by treatment classification (respiratory, pain, and gastrointestinal) and type of inquiry (symptom presentation, direct product request, and both). Standard model diagnostics will be conducted to check for model assumptions. All analyses will be intention-to-treat. Multiple imputation (MI) by chained equations [53] will be applied to account for missing patient outcomes. A total of 30 imputations (including using pharmacy type, age, and sex in the MI model) will be performed. A detailed statistical analysis plan will be developed by blinded investigators before unblinding and locking the study database.

A cost-utility analysis (CUA) and cost-effectiveness analysis (CEA) will be performed through examining the resource use of adult patients in the context of the randomized controlled study designed to investigate the efficacy of AMAS compared with the control group. A healthcare perspective will be applied for the analysis. Costs will be estimated in Australian dollars at the 2018-2019 financial year. Costs during the 2-week follow-up period will be analyzed for all patients included in the cRCT. Costs will be grouped into 4 main categories: (1) pharmacist time, (2) medications, (3) referrals and reconsultation, and (4) training and facilitation costs. The pharmacist cost will consider the working time for a community pharmacist and time consumption to deliver the service. Patient out-of-pocket costs (for all medicines supplied during the 14-day period) will be estimated by the average unit price across pharmacy banner groups. Health service utilization will be based on the cost of medical services recorded in the study, with unit prices sourced from Medicare Benefits Schedule prices, Australian National Hospital Cost Data [54], and the Pharmacy Industry Award [55]. Finally, capital costs for training of pharmacists, facilitation, information technology, and program setup will be counted.

The trial-based outcome measures used for the economic evaluation will be symptom resolution rates and appropriateness of pharmacy care (as a proxy of health gain). Utility values from the literature for symptom resolution and nonsymptom resolution of minor ailments will be used to estimate quality-adjusted life years (QALYs). Other intermediate outcomes will be used to adjust the utilization of resources including referral and reconsultation rates. A decision analytic modeling technique will be used. The model inputs will be informed by data from the trial supplemented with published literature. Results of the CUA will be expressed in terms of an incremental cost per QALY (incremental cost-effectiveness ratio), calculated by dividing the difference in total costs and QALYs between intervention and control groups (incremental costs/incremental QALYs). In addition to the CUA, 2 CEAs will be conducted where the clinical effect measure will be an extra episode of appropriate pharmacy care and extra patient achieving symptom

resolution for their ailment. The cost-effectiveness results will be expressed in terms of extra cost per additional episode of appropriate pharmacy care and extra cost per additional patient achieving symptom resolution.

Ethics Approval and Consent to Participate

This project has been approved by the UTS Human Research Ethics Committee (HREC) (UTS HREC approval number: ETH17-1350). All participants (pharmacies, general practices, and patients) will complete a consent form to participate in this research.

Results

Statistical and economic analyses will be completed in July 2019. Following this, research findings will be disseminated through peer-reviewed publication.

Discussion

Integrated Care

Globally, health care is changing to address a number of challenges including the needs of an aging population, escalation in consumer knowledge and their expectations of the health service, rapid advances in scientific and technical capacity, and the increasing cost of health care [56]. With this, a key issue that needs to be addressed is how to connect services and health care professionals to achieve integrated services for consumers and health professionals as models of care evolve to deliver a person-centered approach [57]. There are excellent services and health professionals all striving to deliver the best possible care, but it is often in a fragmented and siloed manner [2]. The increasing longitudinal care requires both effective oral and *technology-enabled* communication between health care team members.

Innovative thinking and tools are needed to deliver better and cost-effective care. This study is unique, as it enables and evaluates integrated electronic technology systems in Australian primary care for common ailments. This ensures health care providers have access to the best information available to deliver excellent patient care. Although the journey to integrated care is complex, technology can help to support it; this applies to care management and referral (*HealthPathways* [40]), collection of data (*REDCap* [45]), and interprofessional clinician-pharmacist communication (*HealthLink Messaging Software* [43]). This approach offers innovative technologies to move from the traditional health care delivery model, which centers on individual disciplines operating in isolation, to solutions that integrate systems to provide a centralized, complete patient view to health care providers.

This research supports an integrated approach in managing common minor ailments. Drawing on expertise from a range of stakeholders, an AMAS service has been co-designed to complement general practice and promotes collaboration between professions. With the development of agreed clinical *HealthPathways* for a number of common ailments [40], the service aims to standardize practice according to the best available evidence and reduce variations in current practice using a robust framework for referral and treatment. To our knowledge, there is no study investigation or published research relating to a protocolized MAS intervention delivered by community pharmacists for minor ailment presentations in Australian health care. This research will evaluate an Australian MAS reporting on patient outcomes, including health status, and resolution of symptoms and will provide full economic analyses. This evaluation focuses on specific minor ailments for relevant comparisons of both health-related and cost-related outcomes.

Comparison With Literature

The literature internationally suggests that minor ailment services enhance the delivery of primary care, promote efficiencies, and reduce overall health care costs [20]. Pharmacy-based minor ailment services were introduced internationally over a decade ago with the aim of supporting consumers to self-care and provide professional support for conditions that can be self-managed [20]. Previous evidence includes the studies by Paudyal et al [21], Watson et al [16], Aly et al [20], and Rafferty et al [58] reporting on minor ailment services. From the UK perspective, studies have compared outcomes of minor ailment management in settings such as pharmacy, emergency departments (EDs), and general practice [16]. The positive economic impact of MAS has been demonstrated through reduced pressure on other health services and cost-effectiveness compared with more expensive health care services, such as general practice and A&E [16]. Comparatively, Rafferty et al have identified community pharmacy as the most cost-effective option for minor ailment care in Saskatchewan, Canada [58]. The scope of complexity and the varied nature of conditions treated by pharmacists under MASs highlight their skills in being able to assist consumers to self-care, facilitating self-medication, ensuring appropriate use of medicines, and timely medical referral [20]. Comparative evaluations identified in the literature compare general practice or ED settings to the community pharmacy or interventions delivered by health care professionals in ED and GP (ie, physicians or nurses) as a comparator to community pharmacy-based MAS [16,59,60]. Within the various studies, there is no clear distinction between whether pharmacists or members of pharmacy staff deliver the MAS intervention. Our study delineates the role of pharmacist in delivering the MAS intervention, and is not delivered by support staff under pharmacist supervision in the pharmacy.

We report 2 primary outcome measures (appropriate medical referral and appropriate recommendation of nonprescription medicine by pharmacist). Referrals (and importantly, red flag referrals) were a critical point that came up in the codesign process with GPs. GPs wanted to see patients quickly if there were any doubts and ensure patients are being referred in an appropriate and timely manner to the correct health provider. We also wanted to assess pharmacist's impact of MAS on self-medication processes. Further strengths to the study include the adoption of clinical and humanistic outcomes (as secondary outcome measures) recommended by Paudyal et al in a systematic review published in 2018 [61]. Clinical outcomes identified in this international review included symptom status (such as resolution of symptoms, symptom severity, and pattern).

Reconsultation with the GP was identified as a surrogate follow-up measure of clinical outcome assessment. Our study will evaluate reconsultation with the pharmacist, GP, and other health professionals within 14 days for the same ailment. Quality of life outcomes using EuroQoL have also been previously collected in a number of studies [61,62]. Our intervention was developed using available evidence and theory, with key elements. Methods of recruitment, data collection, and study variables were tested during a feasibility and piloting stage. This helped to identify methods to improve recruitment rate, limit documentation time, and confirm relevance and appropriateness of study outcomes to Australian health care.

We present the design of a cRCT in international literature to determine the clinical, humanistic, and economic effectiveness of a protocolized intervention for minor ailments compared with usual care. This study improves on other research evaluating MAS directly using a randomized study design. The randomized controlled trial has a number of important features that make it the *gold-standard* evaluation method [63]. Our choice of cluster randomization at the level of the pharmacy decreases the potential for contamination, as each pharmacist in either the intervention group or the control group will only be providing either AMAS or control, not both. In this respect, the study is novel and will provide information on the impact of the service on clinical, economic, and humanistic outcomes and barriers to implementation compared with usual pharmacy care. However, some limitations to the study should be discussed. Although a cluster randomized design is being used to overcome contamination between study arms, the study design may be susceptible to some methodological biases. Cluster randomized trials often do not, or cannot, conceal treatment allocation. Participants awareness of the allocation can lead to biased recruitment [63]. The Hawthorne effect may also influence research subjects, that is, the consequent effect of being observed or awareness of being studied which can potentially impact on participants' behavior [63]. Finally, one of the main limitations of this type of study is that, by definition, a minor ailment is a self-limiting health problem and implicitly involves resolution, regardless of the intervention performed by the pharmacist. Careful attention has been placed to the design of our cluster trial to minimize the potential for biases.

Conclusions

Collectively, the findings from this study will act as the first stage of implementation of MAS in Australian pharmacy practice and may be extended to facilitate the growing prominence of self-care. The study may also provide groundwork for the optimal design of a MAS intervention tailored for greater patient autonomy and boost the clinician-pharmacist relationship for greater discussion surrounding both the appropriate and inappropriate use of nonprescription medicines. This study evaluates the best possible care to the current level of care provided by pharmacists to patients with common ailments in the Australian population. AMAS presents a key opportunity for pharmacists to intervene, as communication of patient-centric clinical information between health care providers will be essential to support effective patient management in Australian health care.

The delivery of safe and high-quality health services that are fully integrated into the health system are of high importance. Research from high-quality evaluations should be used to inform the strategic direction for health service delivery internationally. Implementation research may be applied to MAS to translate evaluation findings into practice for meaningful improvements in patient care outcomes. This paper is a key step in the dissemination process, outlining the aims and methodology that will be used. Along with providing community pharmacists a framework to patient management and the practical skills to engage patients to self-care and self-medicate appropriately, this study may also contribute to the literature with evidence that an intervention of this nature may lead to more efficient resource use in the provision of primary health care in Australia.

Dissemination Plan

To support this study's contribution to wider knowledge, the research findings will be disseminated through peer-reviewed publications and conferences, both nationally and internationally, targeting service users, health care providers, academics, service commissioners, and policymakers.

Trial Status

The study began in July 2018. A total of 30 community pharmacies were recruited. Pharmacists from the 15 intervention pharmacies were trained. 27 general practices consented. Patient recruitment began in August 2018 and was completed on March 31, 2019.

Protocol Amendments

Any protocol amendments will be submitted to the UTS HREC for approval and noted in the registered protocol at the Australian New Zealand Clinical Trials Registry. Trial participants will be notified should relevant protocol changes be made.

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Authors' Contributions

SDG contributed to background research, manuscript preparation, writing, and review. SDG, VGC, KW, and SB contributed extensively to study design, methodology, review, and editing. KR contributed extensively to the development of the statistical methods, statistical analysis plan, and sample size calculation. All authors have read and approved the final manuscript. The study funders did not have any influence on study design, writing of the manuscript, or decision to submit for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard Protocol Items: Recommendations for Interventional Trials checklist.
[PDF File (Adobe PDF File), 89KB - resprot_v8i8e13973_app1.pdf]

Multimedia Appendix 2
Summary of measurements and study outcomes.
[PDF File (Adobe PDF File), 43KB - resprot_v8i8e13973_app2.pdf]

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Abbreviations

A&E: accident and emergency
AMAS: Australian Minor Ailments Service
CRCT: cluster randomized controlled trial
CEA: cost-effectiveness analysis
CUA: cost-utility analysis
ED: emergency department
GPs: general practitioners
HREC: Human Research Ethics Committee
MAS: minor ailment schemes
MI: multiple imputation
PCF: practice change facilitator

PHN: primary health network
PICF: Participant Information and Consent Form
QALYs: quality-adjusted life years
REDCap: Research Electronic Data Capture
RR: relative rate
UTS: University of Technology Sydney
WSPHN: Western Sydney Primary Health Network

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Protocol

Using Pharmacogenomic Testing in Primary Care: Protocol for a Pilot Randomized Controlled Study

Beatriz Manzor Mitrzyk[1], PharmD, BCPS, BCACP; Reema Kadri[2], MLIS; Karen B Farris[1], PhD; Vicki L Ellingrod[1], PharmD; Michael S Klinkman[2], MS, MD; Mack T Ruffin IV[3], MPH, MD; Melissa A Plegue[2], MA; Lorraine R Buis[2], MSI, PhD

[1]College of Pharmacy, University of Michigan, Ann Arbor, MI, United States

[2]Department of Family Medicine, University of Michigan, Ann Arbor, MI, United States

[3]Department of Family and Community Medicine, Penn State Health Milton S Hershey Medical Center, Hershey, PA, United States

Corresponding Author:
Lorraine R Buis, MSI, PhD
Department of Family Medicine
University of Michigan
1018 Fuller Street
Ann Arbor, MI, 48104
United States
Phone: 1 734 998 7120
Fax: 1 734 998 7335
Email: buisl@umich.edu

Abstract

Background: Antidepressants are used by primary care providers to treat a variety of conditions, including (but not limited to) depression and anxiety. A trial-and-error approach is typically used to identify effective therapy, as treatment efficacy and safety can vary based on the response, which is affected by certain gene types. Pharmacokinetic pharmacogenomic (PGx) testing provides phenotypic classification of individuals as poor, intermediate, extensive, and ultrarapid CYP450 metabolizers, providing information for optimal drug selection.

Objective: The objective of this pilot study is to examine the feasibility, acceptability, and preliminary effectiveness of PGx testing when used after starting a new antidepressant medication.

Methods: We are conducting a pilot study with physicians from 6 Department of Family Medicine clinics at the University of Michigan who are willing to use PGx test results to manage antidepressant medication use. From enrolled physicians, patients were recruited to participate in a 6-month randomized, wait-list controlled trial in which patient participants newly prescribed an antidepressant had PGx testing and were randomized equally to have the results released to their primary care physician as soon as results were available or after 3 months. Patients were excluded if they had been taking the antidepressant for more than 4 weeks or if they had undergone PGx testing in the past. Physician participants completed a baseline survey to assess demographics, as well as knowledge, feasibility, and acceptability of PGx testing for this population. At the conclusion of the study, physician participants will complete a survey to assess knowledge, satisfaction, feasibility, acceptability, perceived effectiveness, and barriers to widespread adoption of PGx testing. Patient participants will complete a baseline, 3-month, and 6-month assessment, and control patient participants will have an additional 9-month assessment. Data collected will include the reason for antidepressant use, self-reported medication adherence, side effects, patient health questionnaire 8-item depression scale, generalized anxiety disorder 7-item scale, 12-Item Short-Form Health Survey, work status or changes, and physician and emergency department visits. PGx knowledge and perceptions (including acceptability and feasibility) as well as demographic information will also be obtained.

Results: We recruited 23 physician participants between November 2017 and January 2019, and 52 patient participants between January 2018 and April 2019. Currently, all physician and patient participants have been recruited, and we expect data collection to conclude in January 2020.

Conclusions: This study will examine the preliminary effectiveness of PGx testing after treatment initiation and determine the feasibility and acceptability of PGx testing for use in primary care. Through this study, we expect to demonstrate the benefit of PGx testing and lay the foundation for translating this approach into use within primary care.

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KEYWORDS

pharmacogenomics; primary care; antidepressive agents

Introduction

Background

Antidepressant medications are the third most commonly prescribed drug type in the United States and are taken by 10.7% of American adults [1]. Although antidepressants may be used to treat a variety of conditions, such as insomnia, neuropathic pain, fibromyalgia, migraine, or menopausal symptoms, depression and anxiety are the most common reasons for using an antidepressant medication. In any given 12-month period, up to 20% of US adults visit their primary care physician for anxiety or a depressive episode [2]. More than half of these adults also have a second depressive or anxiety disorder. Almost 60% of individuals treated for depression (58.5%) are prescribed antidepressants by a general practitioner or family doctor, and about 62% of antidepressants are prescribed by general practitioners [3,4].

Antidepressant medication treatment and achievement of a positive clinical outcome are complicated by several factors. It can take 2 to 4 weeks for symptoms to improve [5,6], and it is possible that the antidepressant medication initially prescribed may require dosage adjustments or even a switch to a different medication because of side effects [7]. Alternatively, another antidepressant medication may be added if symptoms are not improved. Thus, the path to effective antidepressant therapy can be long and complicated. Improving the initiation of antidepressant medications, particularly the time course, will improve patient experiences.

Pharmacokinetic pharmacogenomic (PGx) testing of antidepressant drug metabolism by CYP450 genes and the functional variants (CYP2D6, CYP2C9, CYP2C19, and CYP1A2) may potentially assist with determining drug effectiveness and the possibility of side effects for an individual patient and to ensure the medication(s) prescribed are the best choice for that patient. Individuals can be phenotypically classified as poor, intermediate, extensive/normal or ultrarapid CYP450 metabolizers [8]. Theoretically, metabolism is inversely associated with the antidepressant's clinical effectiveness and side effects. Thus, PGx testing for these genetic variants could be crucial to ensure that antidepressant therapy is tailored to the specific patient. PGx test results should improve the use of antidepressant therapy by minimizing side effects and reducing the number of failed medication trials. These factors in turn should improve medication adherence and antidepressant effectiveness [9]. Although it would be ideal for patients to undergo PGx testing before treatment initiation, waiting for PGx test results, which may take 1 to 2 weeks to return, is not desirable for certain patients, as it would delay treatment and could lead to worsening of their clinical condition. PGx testing early in the treatment process may be beneficial, even if not conducted before treatment initiation. Despite this, the adaptation and implementation of PGx testing into the primary care setting have been slow to occur [10], and PGx testing is not a routine part of primary care practice.

Barriers to adopting PGx testing into clinical practice include issues such as gaps in evidence-based data (insufficient or lacking usefulness), lack of genome-based medicine education, low patient awareness of utility, ethical concerns, inadequate support from prescribers, and inconsistent reimbursement [11]. One key barrier to implementation of PGx testing in primary care is that providers may not be comfortable using PGx data in routine practice, with data suggesting that clinicians commonly override electronic PGx clinical decision support alerts [12]. This suggests a lack of clinician comfort with the integration of PGx data into primary care. In addition, 1 study found that more than 50% of the clinicians surveyed did not expect to use or did not know whether they would use PGx test results in the future [12]. Clinicians may ignore PGx test recommendations if the patient is doing well on the current medication. A possible reason for lack of clinician comfort with PGx testing is limited PGx training [13]. On the basis of this, clinicians may be unprepared to help patients decide if testing is needed, which test(s) to order, or how to interpret and apply test results. Clinician engagement is key to ensuring that PGx test results are effectively adopted into clinical practice and patient care. Data are lacking on the role of PGx testing in primary care to guide antidepressant medication use, and a comprehensive, evidence-based approach is needed.

Study Objective and Aims

The objective of this pilot study is to examine the feasibility, acceptability, and preliminary effectiveness of PGx testing when available just after, or 3 months after, initiating a new antidepressant medication. In terms of feasibility, we are asking physician participants to self-report barriers to PGx testing, as well as whether they would continue to recommend PGx testing. For acceptability, we are measuring physician and patient participants' perceptions of PGx testing and whether they think the information is valuable. Finally, the preliminary effectiveness is assessed using antidepressant medication changes, as well as changes in medication adherence, patient symptoms, and health care utilization.

Methods

Design

We are conducting a pilot study with primary care physicians and their patients. We enrolled physician participants who agreed to participate in a 1-group pre-post design study, using

PGx testing with their enrolled patients. We then recruited patient participants seen by 1 of our participating physicians to enroll in a 6-month, randomized, wait-list controlled trial in which all patient participants newly prescribed (within the last 4 weeks) an antidepressant had PGx testing. The wait-list controlled study design allows us to both have a true control comparison group and also allows us to look at longitudinal effects. Patient participants were randomized equally to 2 groups; one group had their PGx results released to their physician immediately after the baseline visit (intervention), and the other group had results sent to the physician 3 months after their baseline visit (control). All patients enrolled in this trial were recently prescribed one of the target medications by their participating physician. Although PGx test results and any resulting treatment recommendations are made to participating physicians by the study pharmacist, it is up to the physician's discretion to determine if, and how, test results will be used in clinical care.

The primary outcome for effectiveness is the proportion of patients who were prescribed antidepressant medications which are not contraindicated based on PGx test results. Secondary effectiveness endpoints include the change in symptoms or symptom severity as indicated by changes in the 8-item Patient Health Questionnaire (PHQ-8) depression scale [14] and/or Generalized Anxiety Disorder 7-item (GAD-7) scale scores [15], before and after initiation of an antidepressant, and the change in medication adherence as indicated by the change in Adherence to Refills and Medication Scale (ARMS) scores [16]. Feasibility and acceptability will be assessed by responses to the end of study questionnaires developed for the physicians and participants. This study is approved by the University of Michigan (UM) IRBMED Institutional Review Board (HUM00121185) and registered on ClinicalTrials.gov (NCT03270891).

Intervention

PGx test results are provided to the clinical pharmacist through the *Informed PGx* assay by Progenity, LLC. This is a PGx assay that interrogates known CYP450 genes among others, which are related to neurotransmitter function and the pharmacokinetics of psychiatric drugs. This assay uses purified genomic DNA, polymerase chain reaction–based amplification of target regions, sample dilution, and sequencing. The following pharmacokinetic genetic variations detected by this assay are used in this study: CYP2D6 *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *17, *41, and gene duplications; CYP2C9 *1, *2, *3, *4, *5, and *6; CYP2C19 *1, *2, *3, *4, *5, *6, *7, *8, and *17; CYP1A2 *1A, *1C, *1F, *1K, *1L, *3, *4, *5, *6, *7, *8, *11, *15, and *16; CYP2B6 *1, *4, *6, and *18. Polymorphisms in these genes are correlated to rates of metabolism for active or inactive metabolites. On the basis of the presence or absence of polymorphisms, patients are classified as ultrarapid metabolizers, extensive (normal) metabolizers, intermediate metabolizers, poor metabolizers, and unknown metabolizer (unknown). We chose this PGx test because it evaluates variants of CYP450 (CYP2D6 and CYP2C19) that are specific to the primary means of metabolism for certain antidepressant medications. The intervention was designed this way because interpretation of the results and subsequent therapeutic interventions are recommended by Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (which are supported by evidence-based medicine) [16]. Progenity, LLC, no longer offers this PGx test commercially but provided it as a research-use assay for this study.

We provided primary care physicians their patients' PGx test results, interpretation, and antidepressant medication therapy recommendations from our trained clinical pharmacist through a Research Subjective, Objective, Assessment, and Plan (SOAP) note in the electronic medical record (EMR; see Multimedia Appendix 1). The clinical pharmacist uses CPIC guidelines and website recommendations for the target antidepressant medications to support and aid in the interpretation of the PGx test results [17]. The results and interpretation provided are specific to the patient, antidepressant, and any potential interacting coprescribed medications. The delivery of test results through clinical pharmacist replicates routine clinical practice at these sites, as all of our clinics have embedded clinical pharmacists.

Setting

This pilot study is being conducted with physicians and patients from 6 Department of Family Medicine (DFM) clinics at our academic medical center in 5 neighboring communities.

Recruitment and Randomization

To conduct this study, we recruited 2 groups of participants (physician and patient participants).

Physician Participants

We used convenience sampling to identify physician participants. To be eligible for the study, physician participants (1) must be practicing at 1 of the 6 UM DFM clinics, (2) self-report that they were willing to prescribe antidepressants, (3) must be willing to use PGx test results for the management of antidepressant medications, and (4) must be willing to use PGx test results in the treatment of their patient participants enrolled in the study. Physician participants were recruited through a variety of methods, including presentations at faculty business meetings and clinical site staff meetings, as well as targeted emails or letters and follow-up phone calls. All physician participants completed the consent process and will receive no incentives for their participation in this study.

Patient Participants

Once physician participants were enrolled, we recruited participants from among their patients (Figure 1). To be included in this study, patient participants were required to be (1) a patient of an enrolled physician participant; (2) older than 18 years of age; (3) recently prescribed (with last 4 weeks) and taking one of the following medications: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, nortriptyline, bupropion, mirtazapine, or vortioxetine; and (4) willing to undergo a blood draw for PGx testing. Potential patient participants were excluded if they had previously undergone PGx testing or had been taking the antidepressant medication for more than 4 weeks before enrollment. Patients were also excluded if they were not English speaking or were unable to provide their own consent. Target

antidepressant medications for inclusion in this study were selected based on their primary metabolism through CYP2D6 or CYP2C19, or in the case of bupropion, potential for coprescribing with other antidepressants and inhibition of CYP2D6 activity.

We used purposive sampling to identify patient participants. Potential patient participants were identified each week through an automated report from the EMR. Potential participants received 3 targeted recruitment points of contact—initially an email or postal letter, followed by 2 phone calls, emails, or text messages. Patient participants were also recruited through direct provider referral, as well as through posted flyers in the DFM clinics. If a potential participant was eligible to participate in the study, except for the fact that their primary care physician was not yet participating, we attempted to recruit the physician through emails and phone calls.

Procedures

Both physician and patient participants were screened for inclusion and exclusion criteria before obtaining consent and enrollment. Once screened as eligible and enrolled, physician participants completed baseline assessments (Figure 2), and we then started to recruit their patients.

Potential patient participants who were screened as eligible gave consent and then completed baseline assessments, as well as had their blood drawn (3 mL) for PGx testing. Patient participants were then randomized to have PGx test results sent to their enrolled physician as soon as the results were available (intervention) or after 3 months (control; Figure 3).

Initially, randomization of patient participants was set to be stratified by physician to ensure balance within provider; however, given the small patient-to-provider enrollment ratio, stratification by provider was not deemed necessary. Instead, we used a block randomization approach, randomizing patients into 1 of the 2 arms using a block size of 6. The randomization schedule was unknown a priori to researchers enrolling patients and revealed to the patient after completion of the baseline survey.

PGx test results were released to physician participants as a SOAP-formatted research note in the EMR for which the physician participant was alerted through electronic notification. The PGx test results and recommendations provided were for the specific antidepressant—enzyme pair (see Multimedia Appendix 1). At a minimum, a trained clinical pharmacist on the research team met for a phone appointment with the participating physician when their first patient PGx test results were available to provide general, as well as patient-specific, education about the PGx test and results. These consultations were intended to help physician participants interpret PGx test results and guide treatment decisions, if necessary. The clinical pharmacist is available to consult with physician participants at any time during the study, and physician participants are encouraged to contact the clinical pharmacist with questions.

Figure 1. Patient participant flowchart. *Patient was withdrawn from the study 3 months after enrollment because it was discovered that the physician participant listed in the electronic medical record had no previous contact with the patient, and the physician who prescribed the antidepressant did not want to enroll in the study.

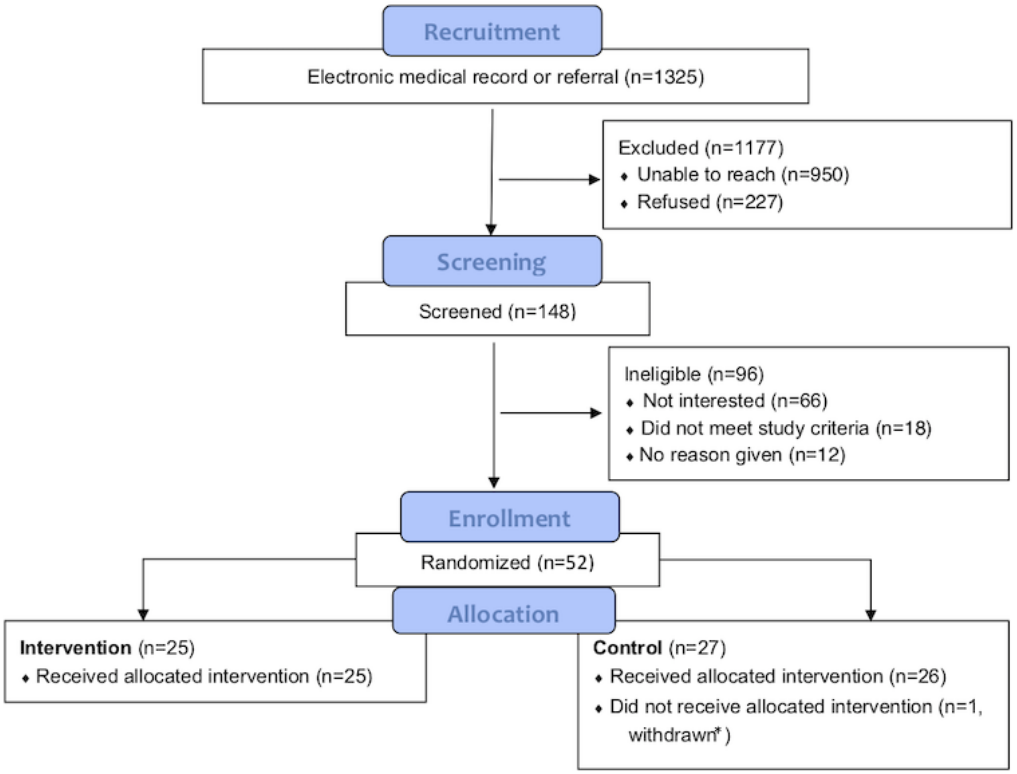


Figure 2. Physician participant study flow. PGx: pharmacogenomic.

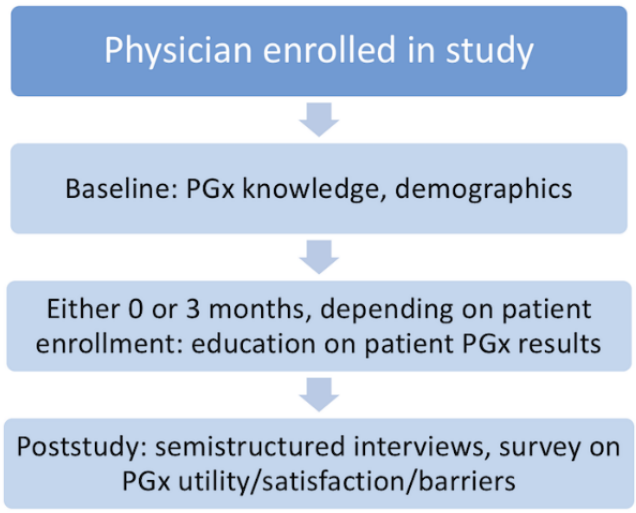
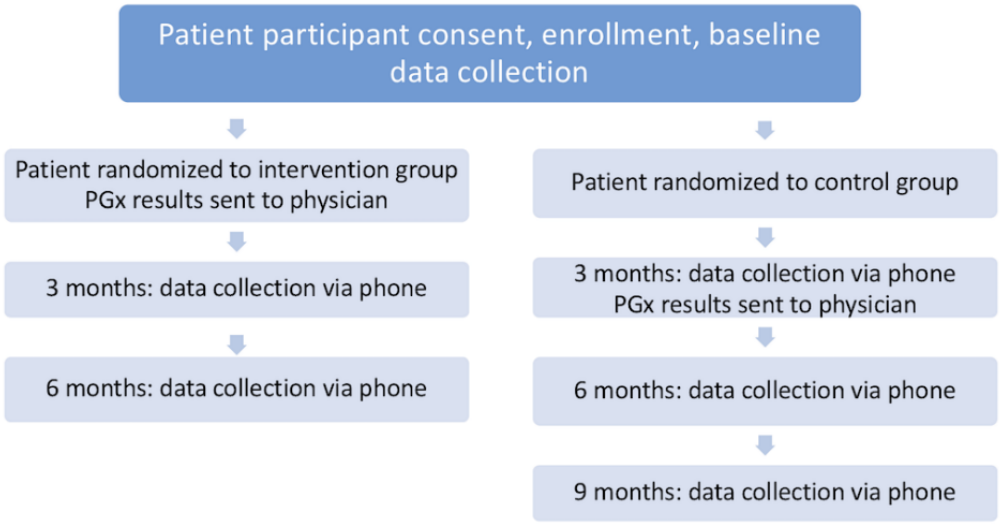


Figure 3. Patient participant study flow. PGx: pharmacogenomic.



No study staff member, including the clinical pharmacist, will provide PGx results to patients; it is up to the physician participants if they choose to share this information with their patients. All intervention patient participants are followed for 6 months, with phone-based follow-up at 3 and 6 months. All control patients are followed for 9 months, with phone-based follow-up at 3, 6, and 9 months.

Data Collection and Measures

Physician Participants

Physician participants completed a self-administered investigator-developed paper survey at baseline. The baseline survey assessed demographics and physician participants' characteristics, knowledge of PGx testing, and perceptions of the feasibility and acceptability of PGx testing in primary care (Table 1).

At the end of the study, physician participants will self-administer a paper survey. This end of study survey contains similar questions as the baseline survey, with the addition of open-ended questions asking whether physician participants recommended PGx testing to other physicians or whether they ordered PGx testing on patients not enrolled in this study. For the open-ended questions, if the physician agrees and would rather give verbal responses to the questions, their responses will be audio recorded for subsequent qualitative analysis.

Feasibility will be assessed by responses to the poststudy questionnaire, which asks physicians to indicate the extent to which they agree with the statements "I think that the process of learning how to use PGx testing in my daily practice would be easy" and "I believe that I could easily incorporate PGx testing into my clinical practice." Acceptability will be assessed by responses to the poststudy questionnaire, which asks physicians to indicate the extent to which they agree with the statements "I see the potential benefit of using PGx testing in my clinical practice" and "If I were to recommend that patients undergo PGx testing, I believe that my patients would choose to be tested."

Table 1. Physician participant measures of feasibility, acceptability, and preliminary effectiveness of pharmacogenomic testing within the investigator developed semistructured interview and survey.

Construct	Assessment time	
	Baseline	Poststudy
Demographic information and characteristics of physicians	✓[a]	—[b]
Knowledge of PGx[c] testing	✓	✓
Acceptability of PGx testing	✓	✓
Utility of PGx testing	✓	✓
Effectiveness of PGx testing	✓	✓
Feasibility of PGx testing	✓	✓
Barriers to PGx testing	✓	✓
Satisfaction with PGx testing	✓	✓

[a]✓ indicates that the construct was assessed.

[b]Not assessed.

[c]PGx: pharmacogenomic.

Patient Participants

All patient participants completed a paper baseline survey, had their blood drawn for the PGx test, and had a pill count of all prescription medications completed at baseline. All patient participants are asked to complete the 3- and 6-month follow-up survey and pill count by phone, and control patients have an additional 9-month follow-up survey and pill count. The baseline survey assessed demographics, participants' characteristics, and health history. All follow-up assessments completed after baseline are telephonic. The baseline and follow-up phone surveys contained questions from the PHQ-8, GAD-7, 12-Item Short Form Survey, Work Productivity and Activity Impairment Questionnaire, the Antidepressant Side-Effect Checklist, and the ARMS. The baseline and follow-up surveys also contained questions from the 3-item self-rated adherence scale, questions about health care utilization, prescribed medications, and ascertained PGx knowledge from an investigator developed survey [14-16,18-20]. The final follow-up survey for each participant includes questions assessing feasibility through responses to statements such as "Did your physician share the PGx test results with you?" and an indication of how much the patient participant agreed with the statement "I understood the PGx test results as explained to me by my doctor." Moreover, acceptability is assessed in the final follow-up survey by responses to indicate how much the participant agrees with the statements "The PGx test results were valuable" and "I would recommend this PGx test to a friend with my condition." We collect a complete list of all medications prescribed from the EMR at all assessments, and pill counts are conducted in person at baseline and over the phone at follow-up assessments. Table 2 presents a complete list of patient participant measures and assessments.

Data Analyses

All survey data, including patient and provider demographics and characteristics, will be analyzed using descriptive statistics to ensure data quality. Independent samples *t* test and chi-square tests will be used to compare patients' characteristics between intervention and control groups. Feasibility, acceptability, and effectiveness based on physician participants' responses and feasibility and acceptability based on patient participants' responses will be analyzed descriptively by assessing the responses to the questionnaire items listed above. Descriptive statistics such as mean and standard deviations, frequencies, and percentages will be used, as appropriate. Open-ended responses will be coded using qualitative thematic text analysis, including any transcripts that result from the recorded survey responses. A team of researchers will analyze and code data independently after initially reading transcripts to gain a general sense of the data, then conduct open coding to identify units of meaning to segments of text, and eventually group codes into major themes and subthemes.

Effectiveness using patient data will be assessed using statistical models. Whether the patient participant is currently prescribed an antidepressant that is appropriate (not contraindicated) based on the PGx test result will be assessed either as soon as results are available or 3 months after the baseline visit, depending on randomization. Logistic regression models, using a generalized estimating equation framework to account for within-subject dependence, will assess the effect of the intervention on the likelihood of being prescribed an appropriate medication by including time, study group, and time by study group interaction as predictors. Secondary effectiveness measures (adherence, depression severity and symptoms, health status, and health care utilization) will be analyzed similarly using linear mixed models, given the continuous nature of the measures. These models will be used to compare the average change in outcomes between study group by including time, study group, and time by study group interaction as the primary predictors of interest for each outcome. For all models, time will be measured both as survey time and time since test results were released to physicians. In the latter, data from the baseline to 6 months period for the intervention group and from 3 to 9 months for the control group will be assessed. All models will be adjusted for patient demographics.

Table 2. Patient participant measures of feasibility, acceptability, and preliminary effectiveness of pharmacogenomic testing.

Construct	Measure	Assessment time			
		Baseline (through paper survey)	3 months (through phone)	6 months (through phone)	9 months (control only; through phone)
General					
Demographic information	Gender, age, and income	✓[a]	—[b]	—	—
Effectiveness					
Depression symptoms and severity	Eight-item Personal Health Questionnaire Depression Scale	✓	✓	✓	✓
Anxiety symptoms and severity	Generalized Anxiety Disorder 7-Item Scale	✓	✓	✓	✓
Functional health status	12-Item Short Form Survey	✓	✓	✓	✓
Missed days of work	Work Productivity and Activity Impairment Questionnaire	✓	✓	✓	✓
Health history	Smoking history, body mass index	✓	—	—	—
Health care utilization	Physician visits and hospital and emergency room admissions	✓	✓	✓	✓
Adverse drug reactions	Antidepressant Side-Effect Checklist	✓	✓	✓	✓
Medication and medication changes	Medications prescribed and number of medication changes	✓	✓	✓	✓
Medication adherence	Adherence to Refills and Medication Scale	✓	✓	✓	✓
Medication adherence	Pill count	✓	✓	✓	✓
Medication adherence	Three-Item Self-rated Adherence Scale	✓	✓	✓	✓
Acceptability and feasibility					
Pharmacogenomic knowledge, perceptions, and experiences	Investigator Developed	✓	—	✓[c]	✓

[a]✓ indicates that the construct was assessed.

[b]Not assessed at that time.

[c]Intervention arm only.

Results

This study is ongoing. Physician enrollment occurred between November 2017 and January 2019, and we recruited 23 physician participants. Patient participant enrollment occurred between January 2018 and April 2019, and we recruited 52 patient participants. We had to withdraw 1 patient because their physician had not seen the patient clinically, nor was the physician the prescriber (see Figure 1). Recruitment for this study is now complete, and we expect patient and physician participant data collection to conclude in January 2020.

At the outset of this study, we sought to recruit patient participants who had recent diagnoses of depression and/or anxiety recorded in their medical record. However, the initial pool of potentially eligible participants was quite small, and enrollment rates were poor. In May 2018, the IRB approved protocol changes to widen the inclusion criteria to any patient with a new prescription for an antidepressant medication from one of the enrolled physicians, regardless of clinical diagnosis, as reflected in this revised protocol. This expansion in inclusion criteria resulted in some participants not having mental health–related diagnoses; however, it is likely that many participants may have undocumented depression or anxiety.

Discussion

Principal Findings

This paper outlines the protocol of a pilot study, which includes a wait-list randomized controlled trial investigating PGx testing

for antidepressant medications in primary care. Despite commercial availability of PGx testing, institutions have been slow to adopt these tests [10]. A recent survey of 10,303 US physicians, of which 39.2% were in primary practice, found that 12.9% of respondents had ordered or recommended a PGx test within the past 6 months, and about 26.4% thought they would in the near future [21].

Despite underutilization, previous work has suggested that PGx test results could improve patient care by reducing the number of side effects, failed medication trials, and time to achieve treatment response [9]. In addition, a recent prospective 12-week study of adult patients with depression and/or anxiety treated in a variety of outpatient clinical settings reported significantly improved clinical outcomes with PGx testing. Bradley et al enrolled 685 adult patients who were randomized to have providers receive PGx test results within 1 to 3 weeks (intervention group) or not receive results (standard of care) [22]. PGx testing included pharmacokinetic and pharmacodynamic variants associated with 10 genes. Patients were either new to treatment or inadequately controlled with antidepressant medications. Patients in the intervention group had response rates (change in depression and anxiety scale scores) that were significantly higher than the standard of care group (odds ratio [OR] 4.72, 95% CI 1.93-11.52; $P<.001$ for depression and OR 1.76, 95% CI 1.03-2.99; $P=.04$ for anxiety). The proportion of patients with at least 1 medication change by week 2 was significantly higher in the intervention group than in the standard of care group (81% vs 64% at 2 weeks, respectively; $P<.001$). However, no difference in the rate of adverse reactions was reported between the study groups. Results from the study by Bradley et al support the use of PGx testing in a diverse adult outpatient population with depression and/or anxiety; however, subanalyses were not reported. Therefore, it is unclear if newly diagnosed patients (with depression and/or anxiety) or those in a primary care setting also significantly benefited from PGx testing. Moreover, this study focused only on patients with depression and/or anxiety, as opposed to all patients taking antidepressant medications regardless of diagnosis.

One of the perceived barriers to utilization of PGx testing in primary care is that clinical utility of the test has not been well established [23]. This is supported by a recent safety statement made by the Food and Drug Administration (FDA), which was made about a year after our study launched. According to the FDA, there is not sufficient evidence to know whether PGx tests influence the effectiveness or safety of antidepressant medication therapy [24]. The FDA recommends that initiation of a medication or medication changes should not be made based on PGx test results because these actions are currently not supported by sufficient scientific or clinical evidence. This highlights the pressing need for more studies to investigate the clinical utility of such tests. Data from this study will provide additional evidence to help address these key points. This trial seeks to contribute to current scientific evidence through assessing the feasibility, acceptability, and preliminary effectiveness of using PGx testing in primary care in persons newly prescribed a target antidepressant.

Limitations

This is a pilot study with a small sample size of patient participants, which limits sample genetic variability (there are more than 50 CYP450 enzymes), the number of abnormal metabolizers, and differences in participant demographics. As previously described, we focused on CYP2C19 and CYP2D6, which metabolize the majority of the most commonly prescribed FDA-approved antidepressant medications and have CPIC guidelines to support therapeutic recommendations. In addition, because this is a pilot study, we are also limited by our relatively small sample size of patient participants who were recruited from a convenience sample of DFM physicians within our institution. Future work is needed with larger sample sizes adequate to detect a difference between groups, ensure demographic saturation, and provide a broader representation of genetic variability.

To increase enrollment, we expanded our protocol inclusion criteria from a diagnosis of depression and/or anxiety to anyone taking targeted antidepressants. The broadening of possible diagnoses increases variability in comorbidities and may change certain patient outcomes. Future studies should limit the diagnoses to avoid these variations.

As with any PGx test, there are limitations to the assay. Direct DNA testing will not detect all variants that result in decreased or increased enzyme activity. Absence of a detectable gene mutation or polymorphism does not rule out that the patient has ultrarapid, intermediate, or poor metabolizer; reduced activity; or reduced response phenotypes for these genes. More research is needed to identify all genetic variations and their possible phenotypes.

This study is being conducted in primary care clinics from 1 academic health center in the United States, which limits the generalizability of the results. Only physicians who were willing to use PGx testing for the selection of antidepressant medications were enrolled, which may be a potential bias, and limits assessment of feasibility and physician willingness to use PGx testing in clinical practice. Ideally, we would have enrolled patients before starting the antidepressant; however, delaying antidepressant therapy while waiting for PGx test results would be unethical.

At our institution, clinical pharmacists have full access to the EMR, are able to write notes, and contact prescribers using direct messaging through the EMR. These interactions are recorded within the EMR. DFM clinics are a Patient-Centered Medical Home and have clinical pharmacists practicing under a collaborative practice agreement within each clinic. Physicians are accustomed to receiving and sending information through the EMR to clinical pharmacists to facilitate patient care. Although not unique to our clinics, this practice model is not commonly used throughout the United States.

Conclusions

This pilot study is designed to assess the feasibility, acceptability, and preliminary effectiveness of using PGx testing in a primary care setting among persons newly prescribed an antidepressant. Physicians' and patients' perceptions of PGx testing, as well as changes in patient medication use and

outcomes, will be evaluated. Results from this study may yield positive effects for all patients on antidepressant medications, not just those with anxiety and/or depression.

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Conflicts of Interest

LRB is obliged to disclose a conflict of interest, as her spouse is an employee and stock option holder at Progenity.

Multimedia Appendix 1
Pharmacogenomic subjective, objective, assessment, and plan note template.
[PDF File (Adobe PDF File), 50KB - resprot_v8i8e13848_app1.pdf]

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Abbreviations

ARMS: Adherence to Refills and Medication Scale
CPIC: Clinical Pharmacogenetics Implementation Consortium
DFM: Department of Family Medicine
EMR: electronic medical record
FDA: Food and Drug Administration
GAD-7: Generalized Anxiety Disorder 7-item scale
OR: odds ratio
PGx: pharmacogenomic
PHQ-8: Patient Health Questionnaire 8-item depression scale
SOAP: Subjective, Objective, Assessment, and Plan
UM: University of Michigan

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Protocol

A Mobile Health Intervention to Improve Hepatitis C Outcomes Among People With Opioid Use Disorder: Protocol for a Randomized Controlled Trial

Karli R Hochstatter[1,2], MPH, PhD; David H Gustafson Sr[3], PhD; Gina Landucci[3], BS; Klaren Pe-Romashko[3], MS; Adam Maus[3], MS; Dhavan V Shah[3], MA, PhD; Quinton A Taylor[2], BS; Emma K Gill[2], BS; Rebecca Miller[2], MSW; Sarah Krechel[4], MPH; Ryan P Westergaard[2], MPH, PhD, MD

[1]Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, United States

[2]Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, United States

[3]Center for Health Enhancement Systems Studies, Department of Industrial and Systems Engineering, University of Wiconsin-Madison, Madison, WI, United States

[4]AIDS Resource Center of Wisconsin, Milwaukee, WI, United States

Corresponding Author:
Karli R Hochstatter, MPH, PhD
Department of Population Health Sciences
School of Medicine and Public Health
University of Wisconsin-Madison
1685 Highland Ave
5th Floor
Madison, WI, 53705
United States
Phone: 1 608 265 9611
Email: khochsta@medicine.wisc.edu

Abstract

Background: People who inject drugs are at a disproportionate risk for contracting hepatitis C virus (HCV). However, use of HCV prevention and treatment services remains suboptimal among people with substance use disorders due to various health system, societal, and individual barriers. Mobile health applications offer promising strategies to support people in recovery from substance use disorders. We sought to determine whether the Addiction-Comprehensive Health Enhancement Support System (A-CHESS), an existing mobile health application for opioid use disorder, could be adapted to improve HCV screening and treatment.

Objective: The goals of this paper are to describe: (1) the components and functionality of an HCV intervention incorporated into the existing A-CHESS system; and (2) how data are collected and will be used to evaluate HCV testing, linkage to care, and treatment.

Methods: People with recent opioid use were enrolled in a randomized controlled trial to test whether A-CHESS reduced relapse. We developed and implemented HCV intervention content within the A-CHESS platform to simultaneously evaluate whether A-CHESS improved secondary outcomes related to HCV care. All A-CHESS users received the HCV intervention content, which includes educational information, private messages tailored to an individual's stage of HCV care, and a public discussion forum. Data on patients' HCV risk behaviors and stage of care were collected through quarterly telephone interviews and weekly surveys delivered through A-CHESS. The proportion of people with opioid use disorder who are HCV untested, HCV-negative, HCV antibody-positive, or HCV RNA–positive, as well as linked to care, treated and cured at baseline is described here. The 24-month follow-up is ongoing and will be completed in April 2020. Survey data will then be used to assess whether individuals who received the HCV-enhanced A-CHESS intervention were more likely to reduce risky injection behaviors, receive HCV testing, link to medical care, initiate treatment, and be cured of HCV compared to the control group.

Results: Between April 2016 and April 2018, 416 individuals were enrolled and completed the baseline interview. Of these individuals, 207 were then randomly assigned to the control arm and 209 were assigned to the intervention arm. At baseline, 202 individuals (49%) self-reported ever testing HCV antibody-positive. Of those, 179 (89%) reported receiving HCV RNA confirmatory testing, 134 (66%) tested HCV RNA–positive, 125 (62%) were linked to medical care and 27 (13%) were treated and cured of

HCV. Of the remaining 214 individuals who had never tested HCV antibody–positive, 129 (31%) had tested HCV antibody–negative within the past year and 85 (20%) had not been tested within the past year.

Conclusions: The A-CHESS mobile health system allows for the implementation of a bundle of services as well as the collection of longitudinal data related to drug use and HCV care among people with opioid use disorders. This study will provide preliminary evidence to determine whether HCV-specific services embedded into the A-CHESS program can improve HCV outcomes for people engaged in addiction treatment.

Trial Registration: ClinicalTrials.gov NCT02712034; https://clinicaltrials.gov/ct2/show/NCT02712034

International Registered Report Identifier (IRRID): DERR1-10.2196/12620

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KEYWORDS

mHealth; eHealth; hepatitis C virus; substance use; continuum of care

Introduction

In 2017, the United States Department of Health and Human Services declared a public health emergency to address the opioid crisis. This state of emergency followed the release of various national reports estimating that, in 2016, 2.1 million people had an opioid use disorder [1], 11.5 million people misused prescription opioids [1], 948,000 people used heroin [1], and 42,249 people died from overdosing on opioids [2], costing the United States approximately 504 billion dollars [3]. Among the many devastating consequences of the opioid epidemic is the increase in prevalence of hepatitis C virus (HCV) through the sharing of injection equipment [4,5]. The estimated prevalence of HCV antibodies among people who inject drugs in the United States is 73% [6]. According to the Centers for Disease Control and Prevention (CDC), from 2004 to 2014 acute HCV increased by 400% among people aged 18-29 and by 325% among people aged 30-39, a trend that was highly correlated with the increase in opioid addiction treatment admissions observed during the same 11-year period [7].

Despite substantial advances in HCV treatment effectiveness and tolerability, use of prevention and treatment services remains low among people with substance use disorders due to various health system, provider, societal, and individual barriers [8,9]. An estimated 72% of young people who inject drugs and are living with HCV are unaware of their HCV infection [10], with only 31% of those diagnosed ever evaluated by an HCV specialist and only a further 8% receiving antiviral treatment [11]. Few evidence-based strategies are available for improving engagement in HCV care for people with a history of injection drug use.

Stigma and discrimination, lack of access to the health care system, and complex health and social needs are among the many obstacles people with substance use disorders encounter that contribute to the observed low rates of engagement in health care compared to the general population [12,13]. Health related smartphone applications have increased in popularity for a variety of conditions [14-16], and there is a growing evidence base suggesting that they may have a role in supporting addiction treatment. They are able to both improve access to comprehensive health services as well as make recovery support, information, and monitoring available almost constantly [17,18]. The Addiction-Comprehensive Health Enhancement Support System (A-CHESS), developed at the University of Wisconsin, is a smartphone application designed to improve recovery from addiction by offering communication with peers and addiction experts, reminders and alerts to encourage therapeutic goals, individualized, addiction related, educational material, and other support services to patients. In a randomized controlled trial (RCT), A-CHESS was shown to reduce risky drinking days and enhance long term abstinence among people with alcohol use disorder, one-third of whom reported illicit drug use [18,19]. A-CHESS also reduced alcohol and opioid use in field tests with the Veterans Administration, drug courts, and among pregnant women in Appalachia [20].

Our research team previously designed and pilot tested another computerized intervention, called Hep-Net [21], to improve HCV-related outcomes among people who inject drugs and participate in harm reduction programs. The Hep-Net intervention targeted four different behavioral domains: (1) undergoing regular HCV screening; (2) using clean drug injection equipment; (3) overdose prevention; and (4) ceasing injection drug use [21]. In the context of an active RCT of A-CHESS to prevent relapse in opioid use disorder [17], our team has integrated content and functionality developed for Hep-Net into the A-CHESS platform. The goals of this substudy are to determine whether HCV-specific services embedded into the A-CHESS program can reduce risky injection behaviors and increase the frequency of HCV testing, linkage to care, and treatment for people engaged in addiction treatment. This paper describes the study protocol implemented to achieve these goals.

Methods

Overall Objectives

The goal of the parent RCT is to assess whether A-CHESS can prevent or delay relapse among people with opioid use disorder who are in early remission and receiving medication assisted treatment (MAT). Individuals with opioid use disorder from two addiction treatment centers in Massachusetts were randomly assigned in a 1:1 ratio to receive either MAT alone (control arm) or MAT and A-CHESS (experimental arm), stratifying on gender and site and balancing on age, level of care, and whether patients had prior substance use disorder treatment. Participants are followed for 24 months, a timeframe informed by prior research to assess the long-term impact of A-CHESS on addiction recovery with adequate power [18,22-24]. The study

design, study population, recruitment, eligibility and screening process, and addiction-related services incorporated into A-CHESS have been described in the parent RCT's published protocol [17]. We developed and implemented HCV intervention content within the A-CHESS platform to simultaneously evaluate whether A-CHESS improves secondary outcomes related to HCV care. In this manuscript, we describe the components and functionality of the HCV intervention incorporated into the existing A-CHESS system and how data are collected and will be used to evaluate HCV testing, linkage to care, and treatment.

A-CHESS contains multiple services designed to address several types of challenges facing people who need treatment and prevention services for addiction. The services are organized around the components of self-determination theory, which postulates that self-motivation and well-being are a function of three innate psychological needs: competence, autonomy, and relatedness [25]. Key A-CHESS services addressing these needs include a call for help function, cognitive behavioral therapy boosters, a GPS location tracker, tailored coping support, a counselor dashboard, coach monitored discussion groups, and HIV or HCV services [17]. A-CHESS provides a medium to disseminate educational information, opportunities to interact with peers and trained counselors, and a platform for collecting participant-level data. These existing features were utilized to collect data on patients' HCV risk behaviors and testing history, and deliver behavior change interventions tailored to the patient's self-reported stage of HCV care.

A variety of study team members have administrative access to the A-CHESS system (eg, coinvestigators, project managers, research assistants and addiction counselors), allowing them to view participant data and send individualized messages. A subset of the investigator team knowledgeable about HCV care (hereafter referred to as HCV research staff) were responsible for conducting the HCV substudy.

HCV Intervention Content

The HCV Care Continuum Model

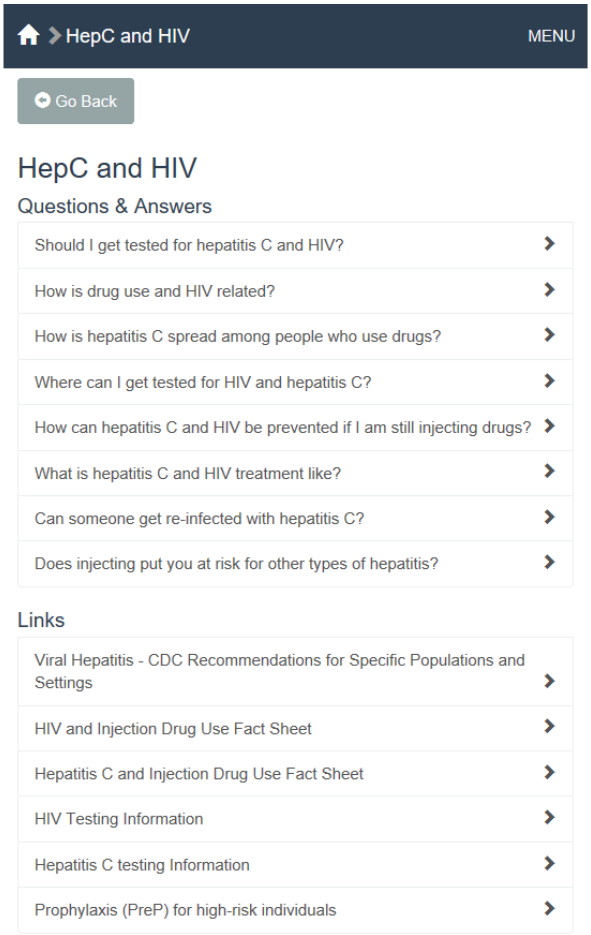
All individuals with A-CHESS received the HCV intervention discussed in this manuscript. The HCV intervention utilizes three A-CHESS components: information dissemination, private messaging, and a discussion forum. The content delivered through these components was developed in consideration of the so-called HCV care continuum: the process of how this disease is ideally managed from prevention, HCV antibody (Ab) screening, HCV RNA confirmation, undergoing HCV evaluation by a medical provider (ie, linkage to care), treatment initiation, retention in care, and then to achieving a sustained virologic response (ie, cure) [26]. Acknowledging that A-CHESS participants may fall anywhere along this continuum, each of the three HCV intervention components provide information and support for all stages of care, making each component relevant to the entire study population.

HCV Educational Information

Significant gaps in knowledge of HCV have been reported among people who use drugs, including a lack of knowledge regarding transmission risks, symptoms and clinical markers, as well as treatment guidelines [27-29]. Understanding that increasing knowledge of HCV is a critical component of public health interventions aimed at reducing the overall burden of HCV, educational materials were incorporated into the A-CHESS system. In addition to various topics related to opioid addiction and recovery, A-CHESS houses HCV-specific information pages that are freely navigable for users. Because injection drug use is also an important driver of the HIV epidemic, accounting for 9% of all new HIV infections [9], A-CHESS provides HIV information as well. This educational content, housed within the information tab of A-CHESS, provides answers to frequently asked questions and links to several fact sheets developed by the CDC (Figure 1). When selecting the option *Where can I get tested for HIV and Hepatitis C?*, A-CHESS users are provided with a list of screening and treatment centers near their place of residence, which is determined by the site at which they enrolled into the study. Links to CDC documents and fact sheets open a Web browser and users are warned that they are leaving the A-CHESS application. To increase awareness of this information and the frequency of views, HCV research staff often reference this content and provide direct links through posts on public discussion boards and private messaging conversations.

News articles related to the intersecting epidemics of opioid injections and infectious diseases are also posted on the information tab (eg, HCV outbreaks among people who inject drugs, the release of new pharmaceutical treatments, important policy changes, and so on). Videos from people affected by these epidemics and expert medical providers working in the field are also on A-CHESS and serve as a powerful means to disseminate information to A-CHESS users.

Figure 1. HCV and HIV educational information available on the information page of the A-CHESS app. HCV: hepatitis C virus; A-CHESS: Addiction-Comprehensive Health Enhancement Support System; CDC: Centers for Disease Control and Prevention.



Private Messaging

Mobile health messaging interventions, such as texting, present promising strategies to increase engagement in health care. These interventions may serve a variety of purposes, including reminders, alerts, education, motivation, and prevention. A large body of literature exists that demonstrates the effectiveness of text message interventions on health outcomes, including the intent to obtain and complete the HPV vaccination series [30-32], uptake of HIV testing [33-35], improved knowledge of sexually transmitted infections (STIs) [36], and increased attendance at HIV appointments [33,37,38]. Although receiving information on HCV and other STIs through text messages has generally been well-accepted by patients [39-41], the effectiveness of mobile health messaging interventions on HCV care engagement have not been well studied. A-CHESS provides a private messaging service that functions very similarly to the standard texting application provided by smartphones, in which users may share content that is visible only to one or more intended recipients. Participants may opt in to receive automated (push) notifications on their smartphones when a private message is received in A-CHESS, when another user posts in a public discussion forum, or both.

HCV research staff use the private messaging feature to send messages related to goals associated with the HCV care continuum. To create a systematic approach for these private conversations, a manual was developed so that individuals in the same HCV stage of care receive the same initial message. Subsequent messages are then guided by each individual's unique response, but towards the same goal of helping each individual advance appropriately along the HCV care continuum. Participants received a minimum of 3 private messages from HCV research staff. When participants responded using the private messaging platform, the HCV research team received an automated e-mail warning them of the new message. This prompted staff to log into A-CHESS and respond at their earliest convince. When staff did not receive a response from the participant, a standardized follow-up message was sent approximately 1 month later.

Because eligibility criteria did not specify a method of opioid use, there are many participants who have not engaged in any injection risk behaviors. If an individual shares that they have never injected drugs and does not believe they are at risk of HCV, research staff express an understanding of their low risk, share information on other means of transmission (eg, sexual contact, tattoos and piercing, and so on), encourage continued preventative actions, recommend one-time testing, and direct them to the educational content to ensure they have information to protect themselves from contracting HCV. Research staff also reference the baseline survey, discussed below, to assess each participant's date of birth. If the participant's date of birth is between 1945 and 1965, the CDC recommendation for all baby boomers to receive a one-time HCV test is shared [42].

Individuals who report being diagnosed with HCV can pose questions to HCV research staff who are familiar with treatment resources in their community. A coinvestigator (an infectious disease physician) maintains a user account, through which they can share health information of general interest to the group and respond to participants' nonurgent health questions related to HCV testing and treatment options.

Discussion Boards

Peer-based education has been shown to be an effective method for reducing risky injection behaviors and preventing HIV transmission [43-45], as well as enhancing HCV treatment knowledge and initiation [46,47]. A-CHESS contains several discussion boards to foster communication of different educational and emotional content. Discussion boards allow users to create and view messages that are accessible to all or only to a subset of study participants. A public group provides a forum for participants to share experiences and engage in conversations on general topics. Separate, treatment specific discussion groups allow participants to interact with other individuals receiving similar forms of MAT, including methadone, buprenorphine, or injectable naltrexone. In these groups, participants are encouraged to discuss experiences that may be specific to their form of MAT, such as side effects, dosage, and adherence challenges. A third public discussion board, named Staying Healthy, is dedicated to discussions surrounding HCV. A-CHESS users use this board to ask infectious disease related questions, share HCV treatment experiences, and discuss barriers to both testing and treatment. HCV research staff also engage in these conversations to remind A-CHESS users of the importance of being tested for HCV, encourage healthy behaviors, and stimulate discussion related to such topics. Upon study enrollment, A-CHESS users create a username of their choice, allowing them to choose an anonymous name that is unidentifiable if that makes them more comfortable when participating in these public discussions. All public discussion threads are monitored regularly by two project managers for appropriate use.

Functionality for Providers

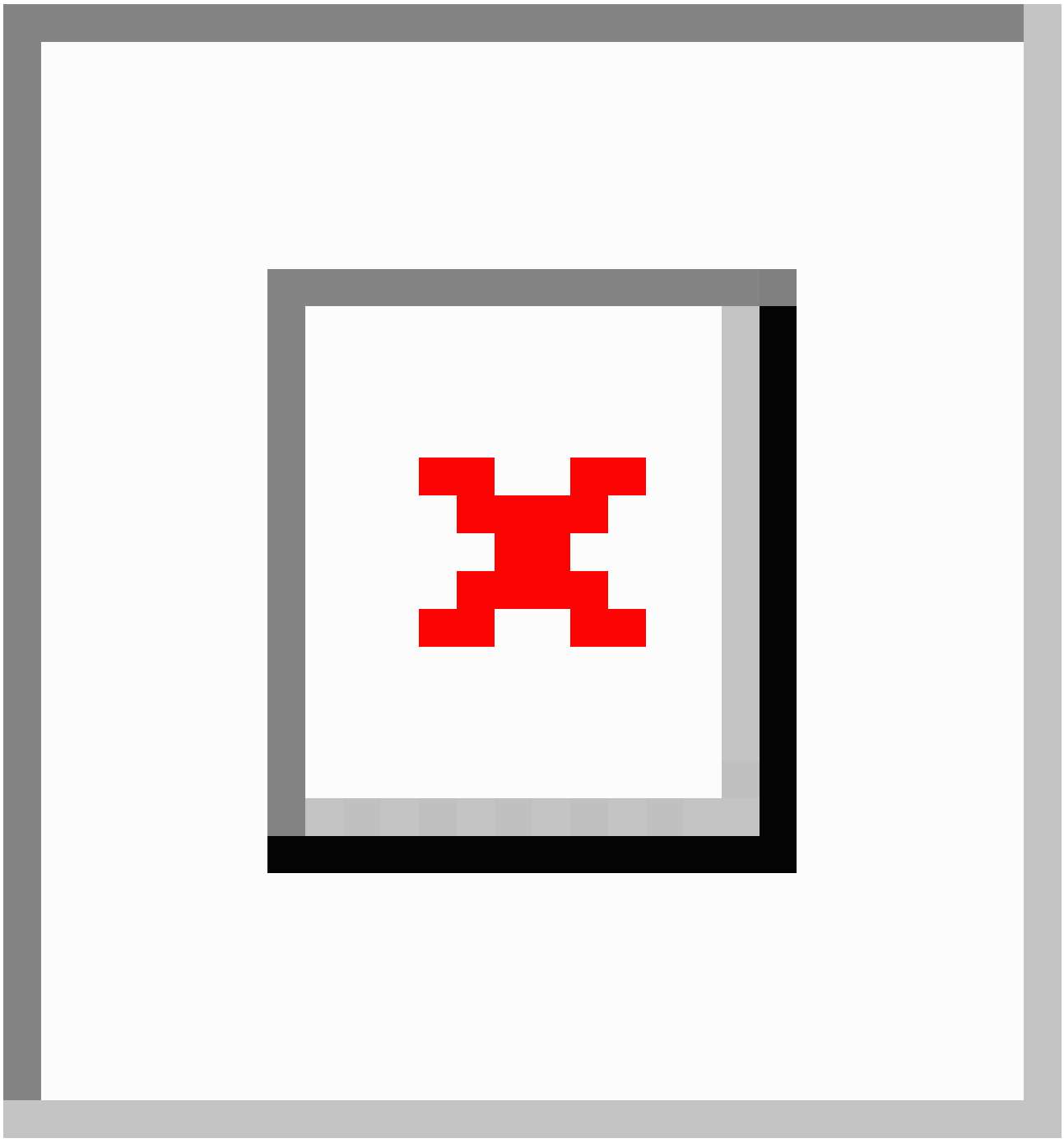
The Moderator Dashboard provides a snapshot to study personnel of key metrics for each study participant, including their treatment center, date of enrollment, HCV status, when they last logged onto the app, A-CHESS use for the past 30 days, the past 25 private messages exchanged between the participant and study personnel, and whether or not the participant viewed the study personnel's most recently delivered private message. Private messages may also be sent directly from the moderator dashboard. Having this information readily available on one screen allows HCV research staff to quickly deliver private messages while accounting for contextual characteristics that are not displayed on the private messaging platform. Staff can use this dashboard to sort and view participants according to who they most or least recently privately messaged, who was most or least recently active on the app, and other individual characteristics. Participants can also be sorted according to their stage in the HCV care continuum in order to facilitate sending private messages in a systematic way. For example, an HCV research staff member could choose to only view study participants classified as HCV-untested, and then send a private message to each individual encouraging testing.

Data Collection Tools

Baseline Study Assessment and Quarterly Telephone Interviews

Baseline questionnaires with both intervention and control participants were conducted over the phone by two study coordinators at the University of Wisconsin-Madison. Information collected at baseline included demographic items, opiate use history, chronic pain, comorbid conditions, and HCV status. Participants were asked at baseline whether they had ever been tested for HCV, as well as the date and result of their last test. If the results from this test were positive, linkage to care and HCV treatment initiation and completion were assessed. Participants were then assigned a baseline stage of HCV care using the logic outlined in Figure 2. Time since last HCV test, whether they had injected drugs since their last test, and if they did not know the answer to questions was taken into consideration when assigning stages of HCV care (see Multimedia Appendix 1). Individuals were also considered HCV-untested if they had not been tested in the past year, if they did not know whether they have ever been tested, or if they had reported injecting drugs since their last HCV test. Both intervention and control participants also received calls from the same two study coordinators quarterly, at months 4, 8, 12, 16, 20 and 24. Follow-up interview questions assessed the same domains as the baseline questionnaire, allowing for the recognition of changes over time.

Figure 2. Questions (in white boxes) asked during the baseline interview that inform the assignment of an HCV stage of care (in black boxes). "a" indicates that individuals were also considered HCV-Untested if they had not been tested in the past year, if they did not know whether they have ever been tested, or if they had reported injecting drugs since their last HCV test. HCV: hepatitis C virus; Ab: antibody.



Weekly Check-In Surveys

In addition to the baseline and quarterly telephone interviews, intervention participants completed short electronic surveys delivered weekly through the A-CHESS app. The brief addiction monitor (BAM) [48], adapted for the smartphone interface using visual analog scales, provided the foundation for weekly assessments of general health status, mood, social support, MAT adherence, and progress with addiction recovery. In addition to these determinants of health, the weekly check-in captured HCV information which could be used to measure progression through the entire sequence of the HCV care continuum and the speed at which individuals received appropriate follow-up testing, got linked to medical care, initiated treatment, and were cured. Logic incorporated into the server back-end of the A-CHESS system was designed to deliver HCV-related questions for the first weekly survey according to the baseline stage of care the participants were assigned during the initial telephone interview. It then updated the HCV stage based on answers to the weekly survey (see Multimedia Appendix 2) and delivered subsequent weekly survey questions according to the newly assigned stage of HCV care. This logic ensured that individuals who previously tested negative for HCV and who continued to engage in risky injection behaviors were asked to repeat testing on a regular basis.

Data Analysis

We used data provided during the baseline telephone interviews to characterize the HCV continuum of care for all participants at the time of enrollment.

The effectiveness of this HCV intervention within the A-CHESS framework will be assessed upon completion of the 24-month follow-up. Four primary outcomes will be examined: undergoing HCV testing, linking to HCV medical care, initiating HCV treatment, and achieving a sustained virologic response. The quarterly telephone interviews, conducted by both intervention and control arms, allows for accurate comparisons between groups. We will conduct four separate binomial logistic regression analyses to assess whether individuals who received A-CHESS were more likely to achieve each of the primary outcomes by 24 months compared to those who did not receive A-CHESS, using an intention-to-treat approach and adjusting for the baseline stage of HCV care. The weekly survey information will allow for a more time-sensitive estimate of the rates at which individuals who use A-CHESS advance along the HCV care continuum.

Upon study completion, the frequency that different HCV components were utilized will also be analyzed to assess how each component is related to improved HCV outcomes among A-CHESS participants. This will allow us to understand the effectiveness of the educational information section, private messaging platform, and public discussion forums individually, as well as estimate the time elapsed between accessing different A-CHESS services and achieving HCV outcomes. Furthermore, although the weekly surveys and quarterly telephone interviews serve as data collection tools, there may be an intervention effect by reminding people to get tested, see a medical provider, and initiate and adhere to treatment. Whether these data collection tools had an intervention effect will be measured by comparing those who did and did not complete the surveys. Understanding the effectiveness of intervention components will inform future, more efficient A-CHESS models.

Results

Participant recruitment occurred during the first 2 years of the study, between April 2016 and April 2018. During this period, 416 individuals were enrolled and completed the baseline survey. Then, 207 were randomly assigned to the control group and 209 were assigned to receive A-CHESS. The 24-month follow-up of enrolled participants is expected to continue until April 2020.

At baseline, 202 individuals (49%) reported ever testing HCV Ab-positive. Of those, 179 (89%) reported receiving HCV RNA confirmatory testing, of which 134 (75%) tested HCV RNA–positive. Among those who reported testing HCV RNA–positive, 125 (93%) reported seeing a medical provider and 27 (20%) had received HCV treatment and achieved a sustained virologic response (Table 1). Of the remaining 214 individuals who had never tested HCV Ab-positive, 129 (60%) individuals reported testing HCV Ab-negative within the past year and 85 (40%) reported not being tested within the past year.

Four (1%) individuals were HIV-positive at the time of study enrollment. All four individuals were on antiretroviral medications and reported strong adherence.

Table 1. Hepatitis C virus continuum of care at baseline (N=416).

HCV[a] status	n (%)
Tested HCV Ab[b]–positive	202 (49)
Tested HCV RNA–positive	134 (75)
Saw a medical provider	125 (93)
Received HCV treatment	27 (20)
Not tested HCV Ab–positive	214 (51)
HCV Ab–negative	129 (60)
Not tested	85 (40)

[a]HCV: hepatitis C virus

[b]Ab: antibody

Discussion

Overview

The overall goal of this novel mobile health system is to support individuals recovering from opioid addiction and improve screening, linkage to care, and treatment rates for HCV, the most common infectious disease burdening people who have a history of opioid use disorder [49]. Baseline data collected from the complete study cohort reveals that nearly half of all study participants (49%) have tested HCV Ab-positive, while few are receiving treatment. An additional 20% of the study population had not been screened for HCV in the past year. These results demonstrate the strong need for HCV screening and treatment interventions among people with opioid use disorders and assures us that this intervention is being implemented among a population with significant potential to benefit. The overall impact that this innovative mobile health system has on HCV-related outcomes will be assessed after 24 months of follow-up interviews and weekly check-in surveys have been collected.

A prior study that examined provider and staff perceptions of A-CHESS implementation identified several facilitating factors

of implementation that also served as important strategies for the implementation of the HCV intervention. Among these factors was the creation of a dedicated internal HCV team with clear roles and responsibilities to lead implementation, the orientation of clients to the content early to build awareness and interest, and the building of a separate discussion forum to stimulate conversation on HCV and build client engagement. These authors also highlighted the importance of collaborating with the mobile app development team to address technical issues [50]. Our close collaboration and weekly meetings with the app development team was crucial for rapidly responding to early implementation issues related to the survey logic and manually changing a participant's assigned stage of HCV care based on private messaging conversations.

Limitations

The generalizability of this study may be limited because participant recruitment was restricted to two addiction treatment centers in the state of Massachusetts. In Massachusetts, fee-for-service and managed care organizations do not have any liver damage, sobriety, or prescriber restrictions [51]. The effect of A-CHESS on HCV outcomes in states with more restricted treatment access may be limited and should be studied independently. Generalizability is also limited to individuals actively and newly engaged in treatment for opioid use disorder. Upon study completion, changes along the HCV care continuum can be compared across subgroups of participants receiving methadone, injectable naltrexone, and buprenorphine, but cannot be compared to individuals receiving no or other treatment regimens, those suffering from other forms of substance abuse, or those at other stages in addiction recovery.

Another limitation of this study is the use of self-reported stages of HCV care. Confusion regarding modes of transmission, the natural history of HCV infection, and interpretation of different HCV tests is common [27-29,52]. In an effort to capture these uncertainties, survey responses allowed individuals to select *I don't know* as an answer choice to HCV questions (See the Multimedia Appendix 1).

At the time of the baseline assessment, 93% of HCV RNA–positive individuals reported they had seen a medical provider for HCV, a level substantially higher than what had been reported in prior studies [26,53,54]. Because the survey questions did not specifically ask whether participants saw a provider specifically to discuss starting HCV treatment, our study may overestimate true linkage to HCV care. Future studies should specify details of the clinical encounter that are of interest. Fortunately, the quarterly follow-up surveys do ask if individuals have received any tests to determine whether they have evidence of liver disease, and these responses will allow us to estimate whether or not individuals received some clinical evaluation to assess their candidacy for HCV treatment after enrollment.

Several intrapersonal characteristics of an individual that are not measured through A-CHESS may influence engagement in care. For example, self-control, organization, and self-awareness are all facets of conscientiousness believed to influence engagement in healthcare [55]. Additionally, responses to mobile health interventions are not expected to be uniform across the study population as individuals differ significantly in their ability and willingness to engage in online communication, a construct that is difficult to measure.

Conclusion

The A-CHESS mobile health system allows for the implementation of a bundle of services and the collection of longitudinal data related to drug use and HCV care among people with opioid use disorders. This study will contribute novel data to better understand whether mobile health applications can support the complex health needs of people affected by the intersecting epidemics of opioid addiction and HCV infection. If effective, this mobile health application has the potential to improve HCV-related outcomes among hard to reach populations that are often disengaged from health care.

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Conflicts of Interest

DG has a shareholder interest in CHESS Mobile Health, a small business that develops Web-based health care technology for patients and family members. All other authors declare that they have no competing interests.

Multimedia Appendix 1

How to assign participants to initial HCV stage based on baseline questionnaire.

[DOCX File, 18KB - resprot_v8i8e12620_app1.docx]

Multimedia Appendix 2

How update HCV stages based on weekly check-in questions.

[DOCX File, 18KB - resprot_v8i8e12620_app2.docx]

Multimedia Appendix 3

Peer-reviewer report from the National Institute on Drug Abuse.

[PDF File (Adobe PDF File), 602KB - resprot_v8i8e12620_app3.pdf]

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Abbreviations

Ab: antibody
A-CHESS: Addiction-Comprehensive Health Enhancement Support System
BAM: brief addiction monitor
CDC: Centers for Disease Control and Prevention
HCV: hepatitis C virus
MAT: medication assisted treatment
RCT: randomized controlled trial
STI: sexually transmitted infection

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Protocol

A Mobile App to Support Parents Making Child Mental Health Decisions: Protocol for a Feasibility Cluster Randomized Controlled Trial

Shaun Liverpool[1*], MSc; Helen Webber[2], BSc; Rob Matthews[2], BA; Miranda Wolpert[1*], DClinPsy; Julian Edbrooke-Childs[1*], PhD

[1]Faculty of Life Sciences, University College London, London, United Kingdom

[2]Create Health, Bristol, United Kingdom

[*]these authors contributed equally

Corresponding Author:
Shaun Liverpool, MSc
Faculty of Life Sciences
University College London
London,
United Kingdom
Phone: 44 2031089888
Email: shaun.liverpool.14@ucl.ac.uk

Abstract

Background: Shared decision making (SDM) is recognized as a person-centered approach to improving health care quality and outcomes. Few digital interventions to improve SDM have been tested in child and adolescent mental health (CAMH) settings. One such intervention is Power Up, a mobile phone app for young people (YP), which has shown some evidence of promise that YP who received Power Up reported greater levels of SDM. However, even though parents play a critical role in CAMH care and treatment, they often feel excluded from services.

Objective: This protocol is for a pilot trial to determine the feasibility of a large-scale randomized trial to develop and evaluate a Web app called Power Up for Parents (PUfP) to support parents and promote involvement in CAMH decisions.

Methods: A 2-stage process, consisting of the development stage and pilot-testing stage of the initial PUfP prototype, will be conducted. At the development stage, a qualitative study with parents and clinicians will be conducted. The interviews will aim to capture the experience of making CAMH decisions, preferences for involvement in SDM, and determine situations within which PUfP can be useful. At the pilot-testing stage, up to 90 parents and their clinicians will be invited to participate in the testing of the prototype. Parents will be randomly allocated to receive the intervention or be part of the control group. This study design will allow us to assess the acceptability and usefulness of PUfP in addition to examining the feasibility of a prospective randomized trial. Clinicians' perceptions of the prototype and how it has influenced parents' involvement in SDM will also be examined.

Results: Recruitment began in January 2019 and is scheduled to last for 10 months. Interviews and baseline data collection are currently in progress. To date, 11 CAMH sites have been recruited to take part in the study. It is anticipated that data collection will be completed by October 2019.

Conclusions: The lack of parents' involvement in CAMH care and treatment can lead to higher rates of dropout from care and lower adherence to therapeutic interventions. There are significant benefits to be gained globally if digital SDM interventions are adopted by parents and shown to be successful in CAMH settings.

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KEYWORDS

shared decision making; mental health; child; adolescent; parents; technology

Introduction

Background

Worldwide, up to 20% of children and adolescents suffer from a disabling mental illness [1,2]. In England alone, 1 in 8 (12.8%) of 5 to 19 year olds have at least one mental health disorder [3]. As a result, families are faced with many decisions, such as how, when, and where to seek help [4]; agreeing on treatment options when more than 1 treatment option is available [5,6]; agreeing on the goals of treatment [7,8]; and agreeing on the diagnostic tests [9]. However, making decisions for young people (YP) with mental health problems can be challenging, as evident by the high levels of disagreement between parents, YP, and clinicians [10-21]. Researchers and practitioners suggest that the implementation of shared decision making (SDM) in child and adolescent mental health services (CAMHS) can be one approach to reduce treatment disagreements [22] and successfully manage the decision-making process that involves balancing multiple perspectives [23,24].

SDM is recognized as a person-centered approach to improving health care quality and outcomes and has been advocated across many health settings, including child and adolescent mental health (CAMH) [23,25,26]. SDM is defined as the communication process that allows service users and service providers to collaborate when making care and treatment decisions [27]. Although there is an increasing demand to include SDM in health care in support of a person-centered approach, attempting to do this in CAMH settings has been met with particular challenges [28].

In adult settings, decisions are *usually* made between the patient and the clinician or, in the case of a triad, the carer is usually another adult. In CAMH settings, the SDM process is unique as it involves a sometimes-complex triad relationship [27,29] between clinicians, children, and parents. Previous studies have mainly focused on the dyad relationships between physicians and patients; therefore, the areas where triad relationships exist have been less understood. When implementing SDM in CAMH, clinicians are forced to moderate highly stressed parents and children and have complex conversations [23].

Researchers highlight common emotional states such as anxiety, distress, sadness, and worry among families involving a child with a mental illness [30-33]. Parents as primary care providers must adopt the responsibilities of caring for a child with mental challenges, which affects their own quality of life [34-36]. Yet, many studies show that parents feel stigmatized and excluded from services [35,37]. Parents feel as if they lack the necessary support from services to help them with supporting their sometimes-unstable child. However, the SDM literature is scarce on whether these emotional factors positively or negatively impact parental decision-making involvement.

As parents are expected to play a critical role in care and treatment, for example, as copatients (family therapy) or as cotherapists (cognitive behavioral therapy), or be the direct focus of the intervention (parent training) [38,39], it is crucial that these parents are involved in the decision-making process. Studies show that involving service users in CAMH care and treatment decisions is associated with improved health outcomes [40] and higher satisfaction with services [41]. Therefore, parents need support to play an active role in the decision-making process.

Improving SDM in CAMH settings can be accomplished when there is an understanding of the factors impacting how parents make or wish to make intervention or care decisions, and when clinicians are able to offer the necessary support for families to be involved in this type of decision making process. SDM includes the notion of a medical encounter as a *meeting of experts*—the physician as an expert in medicine and the patient/parent as an expert in his or her own life, values, and circumstances [42]. British law states that decisions should be made with the child's best interest at heart [43]. Therefore, the decision needs of parents and children should be addressed to accomplish quality decisions, where the quality of the decision is judged as *good* if there is consistency with the decision maker's own values and satisfaction with the decisions made while participating in SDM [44].

Rationale

The prevalence and burden of CAMH on the National Health Service (NHS) is substantial, and supporting large numbers of families at face-to-face sessions can be a challenge [45]; therefore, the use of digital technology can increase access to interventions [46,47]. Mobile technology (ie, mobile phones, tablets, and laptops) use has been on the rise and is estimated to reach 6.1 billion users by 2020 [48]. This offers the opportunity to take advantage of mobile health (mHealth). mHealth is the general term for the use of mobile phones and other wireless technology in clinical practice [49]. Despite the growing number of mHealth apps, the level of awareness and usability of such apps by patients are reported as still relatively low. Nevertheless, the majority of those who use health apps find them to be beneficial and helpful for living a healthier lifestyle [50].

Power Up is an app, co-designed with YP, to empower YP to take an active role in SDM. Power Up has received positive findings, with YP reporting greater levels of SDM after the intervention period [51]. Building on Power Up, this study aims to involve end users in the development of an intervention, called Power Up for Parents (PUfP), to promote SDM and support parents of children and YP accessing CAMHS.

Research Questions

The primary research aim for this feasibility study is to develop and investigate whether it is feasible and acceptable to conduct a prospective randomized controlled trial (RCT) of an evidence-based mobile app to promote SDM in families accessing CAMHS.

The following research questions will be addressed:

1. Is PUfP acceptable and useful for parents and health care professionals?
2. What is the eligibility, participant consenting rates, adherence, and engagement rates of participants using PUfP?

3. Are the outcome measures appropriate and acceptable for a prospective RCT?
4. What are the potential barriers and enablers to conducting a prospective RCT?
5. Which data collection procedures are appropriate and acceptable?
6. What is the scope of the pilot data collected from users and nonusers of PUfP?
7. Can the feedback from PUfP users be used to further refine the prototype for the prospective RCT?

Methods

Design

This a 2-stage study involving a development stage (stage 1) where the intervention will be user-tested by clinicians and parents, and suggestions will be obtained for usage and upgrading of the prototype. The pilot-testing stage (stage 2) is a 3-arm, cluster randomized pilot trial with parents accessing CAMHS.

Study Setting

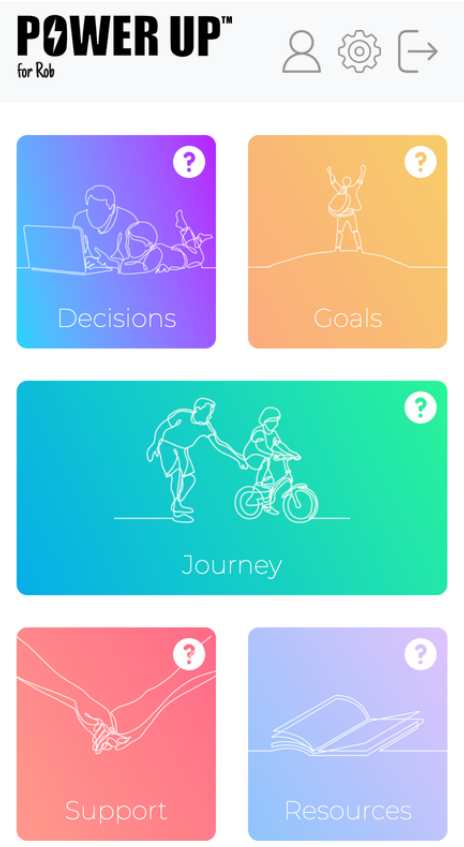
The study team has identified CAMH sites from 18 NHS trusts throughout England. The study team identified and agreed to use 9 London and 9 non-London sites. CAMHS is being used as a broad term for all services that work with children and YP who are experiencing mental health challenges. However, the focus centers around, but is not limited to, specialist CAMHS, where children and YP receive services from a multidisciplinary team that includes psychologists and psychiatrists.

Intervention: Power Up for Parents

The PUfP app is an amended version of the original Power Up app that supports and promotes SDM in CAMH settings. The original Power Up is a mobile app used by YP to empower and encourage them to take an active role in the decision-making process [52,53].

The development of the PUfP prototype was guided by the Workbook for Developing and Evaluating Patient Decision Aids [54] and the Ottawa Decision Support Framework [55]. The prototype (see Figure 1) was informed by a scoping review of existing parent-targeted SDM interventions used in CAMH. A further systematic review was conducted to inform the content of PUfP. We consulted the National Children's Bureau Families Research Advisory Group (FRAG) to obtain input on the study design and how to improve the intervention before the study began. A steering committee involving parents with experience of having a child with mental health problems and the digital lead at the Anna Freud National Centre for Children and Families (AFNCCF) also offered input on the design of PUfP. The content will be screened by various parent groups and professionals before being used in the pilot study. The overall structure of the app's content is as follows.

Figure 1. The home screen.



Decision

This is a decision aid that guides users to seek information about treatment options and the benefits and risks of each option, to track decisions, and to record where more information or support is needed. In addition, as this is a triad relationship, users will be prompted to involve others in the decision-making process by seeking preferences from clinicians, child, or other appropriate persons (see Figure 2).

Goal

This feature can be used in sessions or between sessions to record and track goals as they are discussed with health care professionals and the child. This will allow users to plan and record any questions or concerns they have so that they can address them at the next session (see Figure 3).

Figure 2. The decision tab.

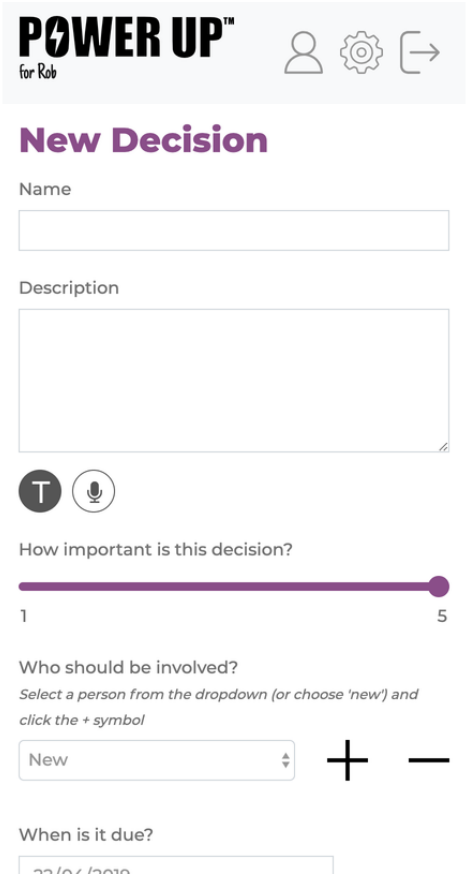
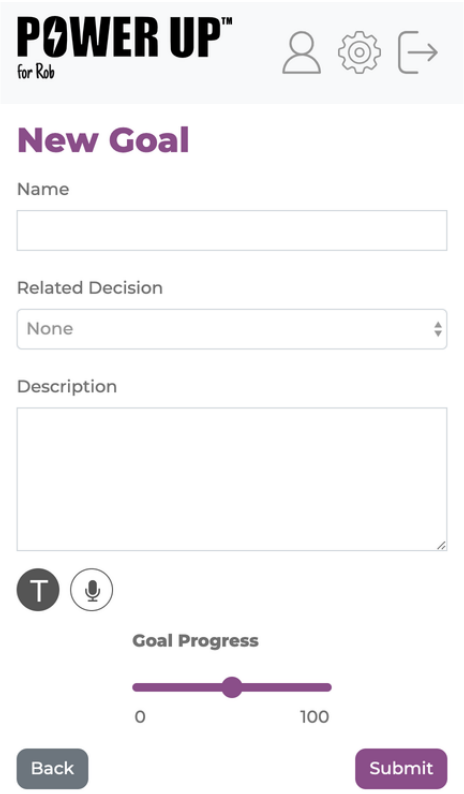


Figure 3. The goal tab.



Journey

This feature allows parents to reflect on their emotions or issues that may be affecting the decision-making process. A parent can decide to share this content with the child and the clinician, and it can be used during and within sessions to keep track of the decision-making journey from user readiness to outcomes. Expectations, experiences, and reflections can all be recorded here using the diary function (see Figure 4).

Support

This section will host a tool to allow parents to identify and express views about various stressors affecting the decision-making process. Users will be able to think about things that are stressful and explore ways to manage these. They can track feelings about decisions and explore where additional emotional support is required (see Figure 5).

Figure 4. The journey tab.

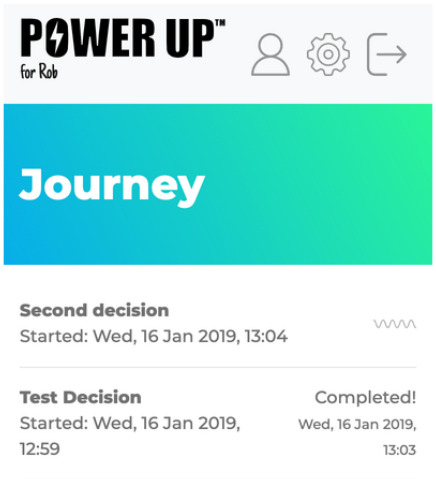


Figure 5. The support tab.

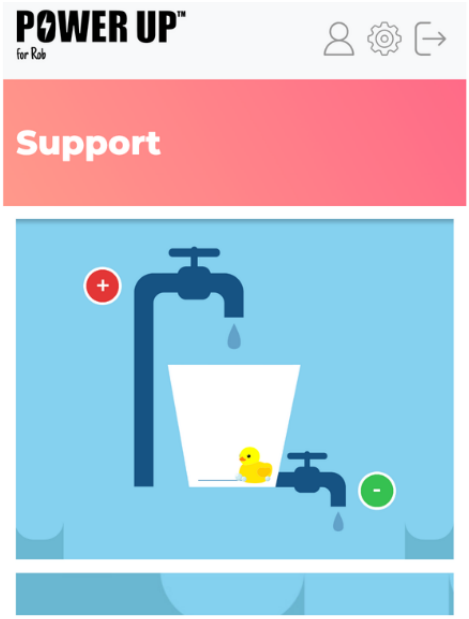
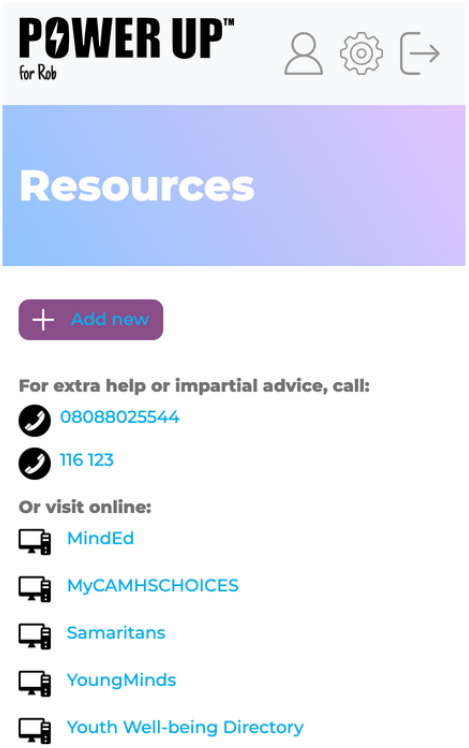


Figure 6. The resources tab.



Resources

This section includes useful contact details that can signpost users to further support and guidance. Parents can also upload their own resources to help with the decision-making process and include contacts that they find most helpful (see Figure 6).

Recruitment

Clinicians

All clinicians at the selected NHS sites will be invited to an information session where they will receive information about the study and be given the opportunity to further assist in developing the inclusion criteria for parent participants and inform the recruitment process. This will allow interested

clinicians to identify themselves to the research team and become early active participants in the trial. Clinicians for the purpose of this study will support the recruitment process by identifying parent participants within their practice and also, as participants themselves, to inform the development of PUfP and provide feedback on its impact.

Parents

On the basis of the inclusion/exclusion criteria agreed at the information session, clinicians will strategically scan their patient list and select suitable participants. At a subsequent meeting with the families, clinicians will solicit interest in participation by sharing some information about the aims of the study. If the family expresses interest in taking part, their contact details will be added to the site's database of potential participants. The key person at the site will supply the researcher with the database of contact details to invite the parents to participate.

Posters will be placed at participating NHS sites, and parents can also voluntarily contact researchers to express interest in participating. Various parent groups will also advertise the study; therefore, parents may also contact researchers without being identified by clinicians. In addition, the research team will visit the selected CAMHS to recruit participants on clinic days. All parents will be screened to ensure they meet the inclusion criteria. The preliminary inclusion/exclusion criteria are given below.

The inclusion criteria included the following:

1. Over the age of 18 years
2. No known diagnosed mental health issues
3. Ability to speak and understand English
4. Parent of at least one young person (>11 years) attending CAMHS

The exclusion criteria included the following:

1. Concurrent and/or involvement in other research that is likely to interfere with the intervention
2. Parents or guardians in cases where the child/young person is being treated under a section of the Mental Health Act

Patient and Public Involvement

Patient and public involvement (PPI) will be conducted throughout the development of PUfP. The opinions and guidance of parent experts and clinicians will be obtained through consultations on the content and the design of the app. We conducted a 3-part consultation session with the FRAG. First, an email consultation round was conducted where the FRAG provided input on the value of PUfP and identified groups of parents that the research team should target for recruitment. Then, the study design and an example of how the intervention might be used were presented to the group. The pros and cons of various modalities for PUfP were discussed along with general thoughts and concerns on the study design. At the final consultation, parents further discussed how service users could use and benefit from the PUfP in practice.

Procedure and Materials

NHS sites were identified through consultations with supervisors and other researchers at the AFNCCF and University College London (UCL). CAMHS were recruited from across England, and a key contact person was identified at each site. The contact person will circulate information about the study to all clinicians. Then clinicians will be invited to an information session where they will receive further information about the study. The team will then begin to identify suitable participants already accessing their services based on the inclusion/exclusion criteria further developed at this session. This will be a transparent process where clinicians will scan their patient list and select suitable participants.

Clinicians will then inquire if the selected families are interested in the study and add them to the site's database of interested participants. Each clinician can continue to add names to the database, and the key contact will provide the updated list of interested participants with their respective contact details as new participants are recruited.

In addition, researchers will attend clinics to distribute flyers and recruit onsite volunteer participants. Parent support groups at the CAMHS services will also be approached, and parents will be given the opportunity to volunteer as participants after information about the study is shared. These forms of recruitment will be guided and informed by PPI participants (parent networks) whose expertise is being sourced to inform the recruitment process.

Stage 1 (Development Stage)

This stage will involve semistructured interviews and focus groups to obtain qualitative data for the design and content of the PUfP prototype. All participants (ie, clinicians and parents) will be sent information sheets and consent forms in advance of the interviews and focus groups. In addition to gathering parents' experiences of decision making in CAMHS, an existing prototype of PUfP will be presented, and suggestions for content and prototype upgrades will be obtained. Focus groups are expected to last up to 90 minutes, and interviews (phone or face to face) to last up to 1 hour. The aim is to achieve saturation or involve a minimum sample of 12 interviews or 2 focus group discussions per group [56,57]. After the first 10 interviews, saturation for this study is reached once no new material emerges after further 3 consecutive interviews [58].

In the focus groups and interviews, participants will review the current prototype on materials supplied by the researcher. Feedback on all aspects of the prototype will be requested, and questions about the additional support needs and recommendations for the upgrade will be asked. In addition, the usefulness of the intervention and preference for modality will be sought. At the end of the focus groups and interviews, participants will be debriefed and advised to contact researchers with any further questions or suggestions via our contact details previously given on the information sheets.

Stage 2 (Pilot-Testing Stage)

The 18 sites identified will be randomly assigned to either control or 1 of the 2 intervention groups. Intervention group 1

(IG1) will receive the prospective version 1 of PUfP, which includes the *Support* and *Resources* features. Intervention group 2 (IG2) will receive version 2 of PUfP without these 2 features. The cluster randomization was completed independently of the research team, using R software guided by the balance algorithm [59]. Participant-level randomization will not be conducted for this study and parents at all selected sites will have a chance to participate in the study. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram (see Table 1) and flow diagram (see Multimedia Appendix 1) illustrates the pathway through the trial, based on the trial protocol (version 1.3, November 14, 2018) approved by the NHS Research Ethics Committee and the Health Research Authority.

Stage 2 involves reinviting previous participants and obtaining informed consent from all the participants. Participants will be identified and recruited in identical ways as in the development stage. Participants will then be assigned to use the prototype and give feedback on usefulness, usability, and acceptability of the intervention. Up to 90 parents, and their respective clinicians, will be invited to participate in this stage with approximately 30 being allocated version 1 of PUfP, another 30 being allocated version 2, and the remaining 30 as the control group, receiving no app but subject to the same battery of questionnaires and treatment as usual. A sample ranging from 10 to 30 per arm should allow for calculations of feasibility and standardized effect sizes that are small to medium [60,61]. Power calculations, based on repeated measures, within – between comparisons among 3 groups for a single measure across two occasions, indicated that a total sample size of 30 would provide a power of 0.8 to detect an effect size of 0.3. Participants will be assigned to an intervention or control group based on the site from which they have been recruited to avoid contamination.

Participants will meet with the researcher at a time convenient to them, to complete a battery of baseline questionnaires, which consists of SDM measures, the experience of service, and decisional conflict measures. Participants will have the choice to complete these online or using paper and pencil. Depending on which group the participants belong to (IG1 and IG2), they will receive help to access the app and be given a guided tour of the app. The parent will then go away and use the app as much as they need to. Participants will complete follow-up measures about 3 months after or at dropout/discharge (whichever comes first).

Table 1. SPIRIT diagram for the Power Up for Parents feasibility trial.

Time point	Study period				
	Enrollment	Pretest	Intervention	Posttest	End of Study
Eligibility screen	X[a]	—[b]	—	—	—
Informed consent	X	—	—	—	—
Allocation	X	—	—	—	—
Interventions	—	—	—	—	—
Intervention Group 1	—	—	X	X	X
Intervention Group 2	—	—	X	X	X
Control Group	—	—	—	—	X
Assessments	—	—	—	—	—
Feasibility outcomes	X	X	X	X	X
CPS-P[c]	—	X	—	X	—
PSDM-Q-Parent[d]	—	X	—	X	—
STAI-AD[e]	—	X	—	X	—
DCS[f]	—	X	—	X	—
ESQ[g]	—	X	—	X	—
PSSUQ[h]	—	—	—	X	—

[a]Schedule and time commitment for trial participants.

[b]Not applicable.

[c]CPS-P: Control Preferences Scale for Pediatrics.

[d]PSDM-Q-Pediatric Shared Decision-Making Questionnaire.

[e]STAI-AD: Spielberger State Anxiety Inventory Form for Adults.

[f]DCS: Decisional Conflict Scale.

[g]ESQ: Experience of Service Questionnaire.

[h]PSSUQ: Post-Study Usability Questionnaire.

Clinicians will also complete an adapted version of the Control Preferences Scale (CPS) so researchers can obtain their perspective on changes in the amount of parental involvement in the child's care and treatment decisions. It may also be important for clinicians to report any changes in the length of appointments or missed appointments and improvements in a child's mental health.

At the end of the pilot-testing phase, participants will share their opinions on the study and, more specifically, on the intervention used and will then be debriefed and thanked for their participation.

Outcome Measures

Stage 1 (Development Stage)

Demographic Characteristics

Participants will be asked both categorical (eg, gender, ethnicity, first language, and relationship to child) and continuous (eg, age) demographics. Demographic data on the patient population will also be collected. This will determine the profile of the families and health care professionals participating in the study.

Interview Topic Guide

The focus groups and interviews will follow a topic guide that aims to allow participants to review the current prototype of PUfP and provide feedback on all aspects of the prototype. Feedback will inform content and design while exploring the decision-making approaches of parents and clinicians. The topic guide will also explore parents' emotions and how they impact the decision-making process. These interviews and focus groups are expected to provide preliminary qualitative input on the acceptability and usefulness of PUfP.

Stage 2 (Pilot-Testing Stage)

Participation Numbers

The number of sites that are approached and the number of sites agreeing to take part will be recorded, in addition to the number of participants agreeing to take part in the study. The proportion of participants completing various parts of the study (ie, consent, pretest, intervention, and posttest) will also be recorded. The app usage rates will also be collected using Google Analytics software.

The Control Preferences Scale for Pediatrics

The Control Preferences Scale for Pediatrics (CPS-P) [62] is an adaptation of the CPS [63]. This tool was originally developed to measure "the degree of control an individual wants to assume when decisions are being made about medical treatment" [64]. The CPS-P consists of 5 different scenarios describing different levels of control preference in decision making. The original scale has been tested in a variety of populations, ranging from the general public to highly stressed groups. The CPS has proven to be a clinically relevant, easily administered, valid, and reliable measure of preferred roles in health care decision making [64]. Permission was obtained to modify and reproduce the CPS-P. Therefore, we also adapted the questionnaire to obtain clinicians' perspectives on how parents preferred to be involved in decisions. Clinicians will be asked to select 1 of 5 statements on whether "the parent leaves all mental health care and treatment decisions about the child to the practitioner" or "the parent shared responsibility for the mental health care and treatment decisions about the child with the practitioner."

Pediatric Shared Decision-Making Questionnaire

The 9-item Pediatric Shared Decision-Making Questionnaire (PSDM-Q-9)—Parent (modified) version measures the extent to which parents are involved in the process of decision making from the perspective of the parent. The measure was developed for use in research and clinical practice. This tool is commonly used for the purposes of evaluation and quality improvement in health care. This measure is being applied in the case of preference-sensitive decisions—that is, when there are several options to be considered before a particular decision is made. This measure has shown face validity and high acceptance. Internal consistency yielded a Cronbach alpha of .938 in a test sample [65].

Spielberger State Anxiety Inventory Form for Adults

The Spielberger State Anxiety Inventory Form for Adults (STAI-AD) is a 40-item self-reported questionnaire commonly used as a measure of trait and state anxiety. It is used in research as an indicator of caregiver distress. The STAI-AD internal consistency coefficients ranged from .86 to .95; test-retest reliability coefficients ranged from .65 to .75 over a 2-month interval [66]. In addition, test-retest coefficients for this measure in another study are rated as highly significant with an intraclass correlation coefficient ranging from .39 to .89 [67].

Decisional Conflict Scale

The 16-item Decisional Conflict Scale was developed to elicit information concerning the decision maker's (1) uncertainty in making a choice; (2) modifiable factors contributing to the uncertainty, such as lack of information, unclear values, and inadequate social support; and (3) perceived effective decision making [68]. This scale quantifies factors that contribute to uncertainty both during the process and at the outcome. Previous studies have shown that the psychometric properties of the scale are acceptable, and it is feasible and easy to administer [68].

Experience of Service Questionnaire

The Experience of Service Questionnaire (ESQ) measures service satisfaction and is widely used in CAMHS in the United Kingdom. The ESQ consists of 12 items and 3 free-text sections looking at what the respondents liked about the service, what they felt needed improving, and any other comments. The satisfaction with care construct will be obtained by adding up items 1 to 7, 11, and 12 [69]. These constructs are important to the study as the SDM process and outcome may impact parents' perception of service satisfaction. On the basis of literature reviews of SDM [70], the research team agreed that the following questions also assess the key components of SDM: (1) I feel that the people who have seen my child listened to me; (2) It was easy to talk to the people who have seen my child; (4) My views and worries were taken seriously and (6) I have been given enough explanation about the help available here [40].

The Post-Study System Usability Questionnaire

The Post-Study Usability Questionnaire (PSSUQ) is a 19-item usability quantification survey developed in 1992 by the IBM Design Centre. The PSSUQ is generally used to quantify the usability of websites, apps, or any software or hardware that users interact with. The questionnaire is a series of statements describing the app that users agree or disagree with using a Likert scale [71]. For this study, the more general term *system* was replaced with the word *app*, and therefore, questions were more targeted, such as "I was able to complete the tasks and scenarios quickly using this app." This measure aims to further assess the usability, appropriateness, acceptability, and feasibility of the overall intervention.

Planned Analysis

Stage 1: Development Stage

Data collected from focus groups and interviews will be analyzed using thematic analysis [72]. Themes will inform the development stage of the intervention by providing the relevant material to inform the content and design of the final version of PUfP. All interviews and focus group sessions will be audio-recorded digitally and transcribed. The computer package Atlas.ti or NVivo will be used to manage the data. Data will be coded using a combination of a priori themes and emergent themes [73].

Stage 2: Pilot-Testing Stage

The data collected will be analyzed with the main aim to reflect on potential improvements to the content of the intervention and informing the overall study design for a prospective RCT. The correlation between demographic data, app use, and outcome measures will be explored to identify target groups. Qualitative and quantitative evaluations will be carried out to examine the acceptability of the intervention as a useful decision aid for parents of children accessing CAMHS. In addition, between-group mean differences at the 2 time points (ie, baseline and follow-up) will be conducted. The standard deviations and intraclass correlation coefficients of the SDM measure will identify the parameters to enable planning for the subsequent trial. The outcome of these analyses will be used to calculate the sample size for the future RCT. Analyses will be conducted using the SPSS software and mostly presented descriptively. The main focus will be on descriptive data, with some exploratory significance testing. The amount of missing data will also be reported for each group.

Outcomes from stages 1 and 2 will be tested against a predetermined set of criteria. Multimedia Appendix 2 summarizes the criteria for assessing the feasibility of a prospective RCT upon completion of the feasibility trial.

Risk Register

Ethical Approvals, Research Governance, and Study Sponsorship

This research project has been ethically reviewed by the London Surrey Research Ethics Committee and approved by the Health Research Authority (IRAS 236277). This study will also be guided by UCL Ethical Standards, the Declaration of Helsinki (2008), the International Conference on Harmonisation Good Clinical Practice, and conducted in accordance with the Department of Health Research Governance Framework for Health and Social Care (April 2005) and the Data Protection Act (2018).

Confidentiality

Interview and focus group recordings will be held securely on a password-protected server at the evidence-based practice unit (using the Data Safe Haven system) until the recording has been transcribed, at which point the recording will be deleted. Transcripts will be held securely under a uniquely identifiable number on the Data Safe Haven system and will be anonymized at the point of transcription. Consent forms will also be kept in secure locked storage, separate from the research data. Anything containing names and contact details will be stored separately and securely from the research data. The data collected during the pilot-testing stage in questionnaire format will only be identifiable by a unique number and will also be kept securely. All paper documents will be kept in secure locked storage, and once the data have been entered into an electronic state, the paper versions will then be shredded and disposed of according to UCL's standards for disposing of confidential waste. Appropriate access controls will be in place to ensure that access to confidential research information is restricted to the main researcher (SL) and immediate supervisors (JEC and MW). All data will be collected, handled, and stored in accordance with local and national information governance procedures, including the Data Protection Act (2018).

Safeguarding

To protect both the participants and researchers, safeguarding procedures of UCL/AFNCCF, in addition to the NHS site procedures, will be strictly adhered to. Safeguarding protocols will be followed if at any point of the research a participant reveals information that suggests he/she is of serious risk to themselves or others. If any participant becomes distressed or too emotional during the interviews, they will be treated with compassion and empathy by trained/experienced researchers and signposted to further help if necessary. The content of the questionnaires have been reviewed to ensure that the standardized measures that are least likely to cause further burden are selected.

Recruitment

Parents and clinicians will need to set aside time for participating in interviews/focus groups. The researchers will remain flexible, and parent participants will be offered prospective travel reimbursement where necessary. Participation will remain voluntary to avoid any burden to participants, and all participants at every stage will be required to give informed consent. Details of their role in the study will be given both orally and via the information sheets, and all questions will be addressed. Participants can opt out at any stage of the study if they feel uncomfortable.

Intervention

The actual use of the app may become an inconvenience for the parent or clinician. Owing to the co-design approach taken, the features should be something that parents are interested in using. By taking this approach, it is less likely that the use of the app

will be seen as an inconvenience. In addition, clinicians are allowed to be flexible with the use of the prototype during sessions and therefore can manage any time strains.

Results

Recruitment began in January 2019 and is scheduled to last for 10 months. Interviews and baseline data collection are currently in progress, and to date, 11 CAMH sites have been recruited to take part in the study. It is anticipated that data collection will be completed by October 2019.

Discussion

To our knowledge, this is the first feasibility study to pilot-test an interactive parent-targeted digital SDM tool across CAMHS in England. This 2-stage research project and its findings will inform the development and testing of a parent-targeted SDM Web app to be used in CAMHS. It will target parents/primary caregivers of children seeking various mental health services. PUfP is expected to offer the necessary support parents need when making decisions for/with children with mental health challenges.

One advantage to this study's approach is that parents and clinicians themselves get to shape a tool that caregivers, clinicians, and other service providers and users may access in the future. Participants may find taking part in research to be rewarding, as they contribute to the development of knowledge that may benefit themselves and others. Parents will feel supported and empowered to make informed choices and feel included in the SDM process alongside their child and the health professionals. This approach coincides with the National Institute for Health and Care Excellence guidelines on service users having the right to be involved in discussions about treatment and care [25]. This research will have implications for the use and implementation of digital interventions within the NHS and future research in the area of SDM as a triad process in CAMHS.

Finally, the findings from this feasibility study will inform the planning of a prospective RCT. The larger study will add to this initial understanding of how the implementation of PUfP can aid in the promotion of SDM in CAMHS while reducing parents' feeling of exclusion from the decision-making process. The prospective RCT may also be able to highlight other areas PUfP can impact, for example, on decreasing waiting times if parents have quicker access to support. This study and the prospective RCT can have research, policy, and practice implications for how SDM is managed in CAMHS with the use of technological interventions.

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Authors' Contributions

MW and JEC developed the initial idea for the intervention and were involved in the funding application process with TEAM. SL worked with the staff at Create Health (HW and RM) to develop, adapt, and refine PUfP. SL drafted the protocol, and all authors revised the manuscript and have read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Go No-Go Criteria.
[PDF File (Adobe PDF File), 336KB - resprot_v8i8e14571_app1.pdf]

Multimedia Appendix 2
Flow diagram of the Power Up for Parents (Stage 2) feasibility trial.
[PDF File (Adobe PDF File), 179KB - resprot_v8i8e14571_app2.pdf]

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Abbreviations

AFNCCF: Anna Freud National Centre for Children and Families
CAMH: child and adolescent mental health
CAMHS: child and adolescent mental health services
CPS: Control Preferences Scale
CPS-P: Control Preferences Scale for Pediatrics
ESQ: Experience of Service Questionnaire
FRAG: Family Research Advisory Group
IG: intervention group
mHealth: mobile health
NHS: National Health Service
PPI: patient and public involvement
PSSUQ: The Post-Study System Usability Questionnaire
PUfP: Power Up for Parents
RCT: randomized controlled trial
SDM: shared decision making
STAI-AD: State-Trait Anxiety Inventory for Adults
UCL: University College London
YP: young people

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Protocol

Examining the Impact of a Personalized Self-Management Lifestyle Program Using Mobile Technology on the Health and Well-Being of Cancer Survivors: Protocol and Rationale for a Randomized Controlled Trial (The Moving On Study)

Jenny M Groarke[1], PhD; Janice Richmond[2], PhD; Mary Grace Kelly[2], MSc; Jenny McSharry[3], PhD; AnnMarie Groarke[3], PhD; Tommy Kerr[2], MSc; Nina Singaroyan[2], MSc; Owen Harney[3], PhD; Charlene Haughey[2], D Clin Psych; Liam Glynn[4], MD; Eimear Masterson[2], BSc; Aoife O Donnell[2], BSc; Karen Duffy[2], MD; Jane Walsh[3], PhD

[1]School of Psychology, Queen's University Belfast, Belfast, UK, Belfast, United Kingdom

[2]Letterkenny University Hospital, Donegal, Ireland

[3]School of Psychology, National University of Ireland, Galway, Galway, Ireland

[4]Health Research Institute and Graduate Entry Medical School, University of Limerick, Limerick, Ireland

Corresponding Author:
Jenny M Groarke, PhD
School of Psychology, Queen's University Belfast, Belfast, UK
David Keir Building
Belfast,
United Kingdom
Phone: 44 0289097 ext 4886
Email: j.groarke@qub.ac.uk

Abstract

Background: Cancer survivorship in Ireland is increasing in both frequency and longevity. However, a significant proportion of cancer survivors are overweight. This has negative implications for long-term health outcomes, including increased risk of subsequent and secondary cancers. There is a need to identify interventions, which can improve physical and psychological outcomes that are practical in modern oncology care. Mobile health (mHealth) interventions demonstrate potential for positive health behavior change, but there is little evidence for the efficacy of mobile technology to improve health outcomes in cancer survivors.

Objective: This study aims to investigate whether a personalized mHealth self-management lifestyle program is acceptable to participants and can improve physical and psychological outcomes of a subgroup of cancer survivors with increased health risks related to lifestyle behaviors.

Methods: A sample of 123 cancer survivors (body mass index >25 kg/m^2) was randomly assigned to the control (n=61) or intervention (n=62) group. The intervention group attended a 4-hour tailored lifestyle information session with a physiotherapist, dietician, and clinical psychologist to support self-management of health behavior. Over the following 12 weeks, participants engaged in personalized goal setting to incrementally increase physical activity (with feedback and review of goals through short message service text messaging contact). Objective measures of health behavior (ie, physical activity) were collected using Fitbit (Fitbit, Inc). Data on anthropometric, physiological, dietary behavior, and psychological measures were collected at baseline (T0), 12 weeks (T1; intervention end), and 24 weeks (T2; follow-up). Semistructured interviews were conducted to explore the retrospective acceptability of the Moving On program from the perspective of the recipients.

Results: This paper details the protocol for the Moving On study. The project was funded in August 2017. Enrolment started in December 2017. Data collection completed in September 2018. Data analysis is underway, and results are expected in winter 2019.

Conclusions: The results of this study will determine the efficacy and acceptability of an mHealth intervention using behavior change techniques to promote health behaviors that support physical health and well-being in cancer survivors and will therefore have implications for health care providers, patients, health psychologists, and technologists.

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KEYWORDS

mHealth; SMS; activity tracker; behavior change technique; health behavior change; obesity; cancer

Introduction

Background

In Ireland, an average of 37,000 new cases of cancer are diagnosed each year, and it is predicted that the incidence of cancer will double by 2040 [1]. At the same time, cancer survivorship in Ireland is increasing, with survival at 5 years from diagnosis having increased to 62% overall [1].

There is consistent evidence of a positive association between being overweight or obese and all-cause morbidity and mortality [2]. High body mass index (BMI), poor diet, and lack of physical exercise are identifiable risk factors for cancer development, and in cancer survivors, these factors can increase the risk of a secondary cancer or a subsequent primary cancer [3,4]. Cancer and cancer treatment can result in physical inactivity and loss of muscular strength [5]. Previous research has identified that approximately 50% of cancer survivors are overweight [6], and research in women has linked obesity to a 46% increased risk for eventual development of distant metastases [7]. Cognizant of the consequences of morbidity and mortality, there is a need to facilitate rehabilitation of cancer survivors to reduce BMI and improve physical and psychological health.

Mobile health (mHealth) is the practice of medicine and public health supported by mobile devices (eg, mobile phones, smartphones, tablets, mobile apps, and wearable monitors). The use of mobile apps has been associated with significant reductions in weight and BMI [8]. Mobile technology has also been shown to assist in behavior change for physical activity, and it offers much potential for sustainable lifestyle change, as it provides feedback to consolidate self-management habits [9,10]. Therefore, mHealth tools may help meet the need to provide cost-effective behavior change interventions that support weight loss.

Although mHealth interventions hold significant potential, adopting a theory and evidence-based approach to intervention design is critical [11]. The Behavior Change Wheel (BCW) is a synthesis of 19 frameworks of behavior change [12]. The BCW, together with the Behavior Change Technique (BCT) Taxonomy, a standardized list of the active ingredients of behavior change interventions [13], enables researchers to develop and describe complex interventions in a systematic and rigorous way.

Systematic review evidence suggests that the use of relevant BCTs significantly increased the success of weight loss programs [14]. A systematic review of existing healthy eating and physical activity interventions identified the BCTs *self-monitoring* in combination with *goal setting* and *feedback* as the most effective [15]. A recent meta-analysis of 30 randomized controlled trials (RCTs) to increase physical activity among cancer survivors reported that certain BCTs (*prompts*, *social rewards*, and *graded tasks*) were associated with larger increases in physical activity. Interventions using a greater number of BCTs were associated with greater physical activity gains [16]. As such, these BCTs should be considered for inclusion in interventions aiming to increase physical activity.

Studies have found that both mHealth interventions and the inclusion of relevant BCTs can lead to positive health behavior change and weight loss and therefore, gains may be particularly great when mHealth and BCTs are combined. Digital interventions including a greater number of BCTs were found to have larger effects on health behavior change than interventions with fewer BCTs [17]. A review and meta-analysis of studies using activity monitors found that in people with obesity, physical activity increases were greatest when the BCTs *goal setting* and *feedback* were incorporated in the mHealth intervention [18]. A systematic content analysis of the BCTs provided by wearable activity monitors concluded that most monitors included *self-monitoring*, *goal setting*, and *feedback* [19]. More generally, the review by Michie et al [15] found these to be the most effective BCTs for promoting healthy diet and physical activity.

mHealth interventions incorporating relevant BCTs have the potential to support weight loss [16,17,19]. However, there are a limited number of mHealth interventions using BCTs with cancer survivors. In the previously mentioned meta-analysis of 30 physical activity RCTs for cancer survivors [16], only 2 studies [20,21] used digital technologies as the mode of delivery (MOD) for BCTs to increase physical activity. The study by Bantum et al [20] found that a 6-week Web-based self-management workshop increased self-reported strenuous physical activity of cancer survivors. The other study with breast cancer survivors used *prompts* delivered by email in declining frequency over 12 weeks and reported significant group differences in self-reported physical activity levels postintervention [21]. These studies highlight that there is potential for digital health interventions to improve lifestyle behaviors among cancer survivors. Yet, more evidence is needed regarding the effectiveness of interventions using mobile technologies with cancer survivors on objective health outcomes.

Aims and Objectives

The aim of this multidisciplinary research study is to investigate whether or not a personalized mHealth (mobile technology) self-management lifestyle program can improve physical and psychological outcomes of a subgroup of cancer survivors with increased health risks related to lifestyle behaviors. More specifically, this project will examine the impact of lifestyle advice and personalized goal setting compared with standard medical care on both clinical and psychological outcomes. Furthermore, this study will explore the acceptability of this intervention to participants receiving the Moving On program.

Methods

Study Design

A 2-arm, parallel, open-label RCT design was used to investigate the impact of a personalized mHealth intervention versus standard care on primary and secondary health outcomes. Eligible participants were randomized to either the intervention or the standard care control condition using a computerized random number generator. Assessments took place before randomization (T0; baseline), at 12 weeks (T1; intervention end), and at 24 weeks (T2; follow-up). The study was not blinded.

On completion of the study, a series of semistructured interviews were carried out to assess retrospective acceptability of the intervention from the perspective of the recipients. Purposeful maximum variation sampling was used. The theoretical framework of acceptability of health care interventions was used as a topic guide [22]. Specifically, open-ended questions were asked regarding participant's affective attitude toward the intervention, the intervention's coherence, participant burden, perceived effectiveness, and participants' sense of self-efficacy.

Study Setting

Recruitment and assessments took place in Letterkenny University Hospital, Co. Donegal, Ireland.

Ethics Approval

The design of this study was approved by the National University of Ireland, Galway Research Ethics Committee on September 12, 2017 (Ref: 17/MAY/20), and by the Research Ethics Committee at Letterkenny University Hospital on May 2, 2017.

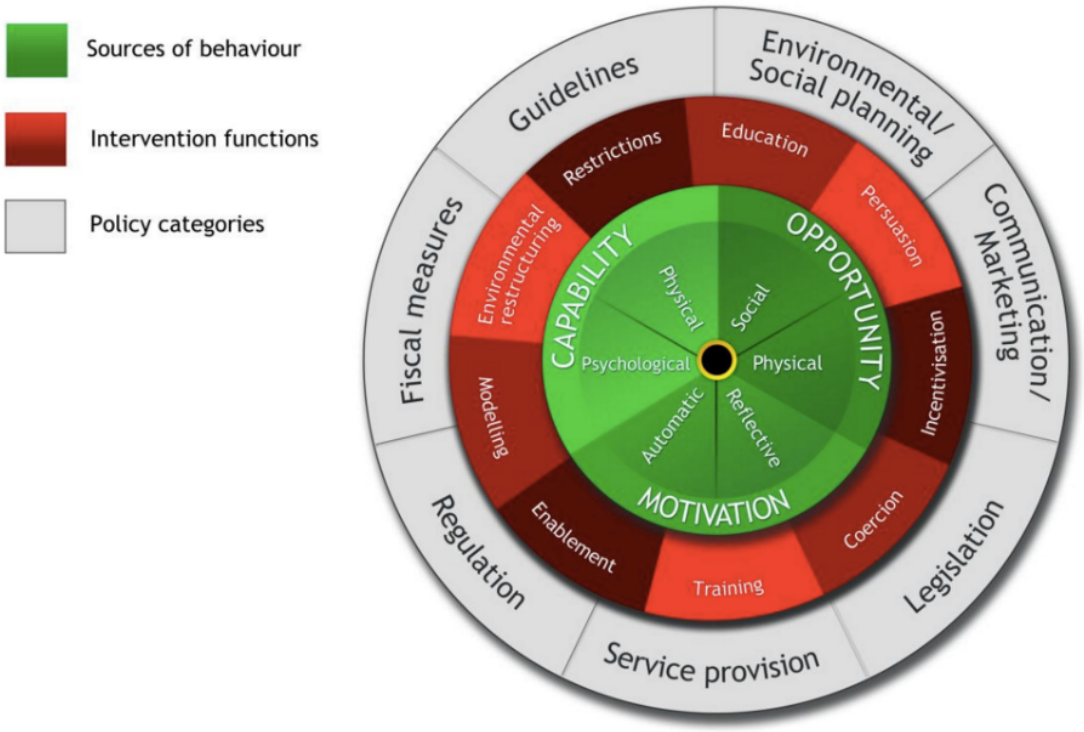
Intervention

Development

The Moving On program is an intervention using BCTs and mobile technology to promote self-management of lifestyle behavior among cancer survivors who are overweight. The intervention was designed following the BCW [12] presented in Figure 1. The COM-B system at the center of the wheel proposes that people need the capability (C), opportunity (O), and the motivation (M) to perform a behavior (B). The second and third layers of the wheel describe intervention functions, the broad categories of means by which an intervention can change behavior, and policy categories that can support behavior change. The final step in intervention design is to identify BCTs and modes of delivery likely to be effective based on previous research.

Two behavioral targets were identified to improve health and well-being outcomes, which were to increase physical activity and improve diet. The functions of the first component of the intervention are *education* and *training*. The lifestyle information and education session aims to increase participants' psychological capability to change behavior by imparting knowledge and skills to increase healthy eating and exercise. The function of the second intervention component (goal setting) was *enablement*. Participants were provided with a Fitbit activity tracker influencing their opportunity to increase physical activity. Participants also received short message service (SMS) text messaging contact from the behavioral science researcher regarding physical activity goals aiming to influence their motivation to increase exercise.

Figure 1. The behavior change wheel reproduced with permission from Michie et al.



Next, a detailed intervention plan was developed and described using the BCT Taxonomy version 1 [13]. Key BCTs were selected on the basis of successful application in previous interventions targeting physical activity and dietary behavior change [14-16,18]. The full intervention specification detailing the content (BCTs) and MOD [23] for each BCT are described for both components of the intervention in Tables 1 and 2. The lifestyle information and education session was delivered primarily through face-to-face human contact in real time to groups of participants. In contrast, the goal setting intervention was delivered through human contact at a distance using nonautomated SMS text messages and facilitated using digital wearable technology.

Table 1. Description of intervention content of the lifestyle information and education session (week 1) specified in terms of the Behavior Change Technique Taxonomy Version 1 and the Mode of Delivery Taxonomy.

BCT[a] and definition	Application in this study
Goal setting (outcome): set or agree on a goal defined in terms of a positive outcome of wanted behavior.	All participants enrolled in the research study are encouraged to lose weight by increasing their level of physical activity and improving their diet; MOD[b]: human and face-to-face.
Provide information on consequences of behavior to the individual: provide information (eg, written, verbal, and visual) about health consequences of performing the behavior.	Participants are given information on physical activity and healthy eating tailored to cancer survivors. For example, that high-impact activity, such as walking, is safe for cancer survivors.
Demonstration of the behavior: provide an observable sample of the performance of the behavior.	A series of physical exercises are demonstrated by the physiotherapist, and participants are shown how to use body parts (eg, hand) as a visual guide for healthy portion size. Information is summarized in a written information sheet to take home; MOD: human and face-to-face; MOD: printed material and leaflet
Provide instruction on how to perform the behavior: advise or agree on how to perform the behavior.	A series of physical exercises are demonstrated by the physiotherapist, and participants are shown how to use body parts (eg, hand) as a visual guide for healthy portion size. Information is summarized in a written information sheet to take home; MOD: human and face-to-face; MOD: printed material and leaflet
Problem solving: analyze, or prompt the person to analyze, factors influencing the behavior and generate or select strategies that include overcoming barriers and/or increasing facilitators.	Using a worksheet, each participant is prompted to record their goal, identify barriers to their goal, define the barrier in terms of it being a personal, environmental, social, or organizational barrier, and finally to identify strategies to overcome each barrier identified; MOD: human and face-to-face
Goal setting (behavior): set or agree on a goal defined in terms of the behavior to be achieved	Participants agree to gradually increase their physical activity level, including their average daily step count
Action planning: prompt detailed planning of performance of the behavior, must include at least 1 of context, frequency, duration, and intensity	Each participant is prompted to make a plan to increase their physical activity level toward the recommended 10,000 steps per day and perform the exercises recommended by the physiotherapist at a time/place of their choosing from a choice of schedules; MOD: human and face-to-face

[a]BCT: behavior change technique.

[b]MOD: mode of delivery.

Table 2. Description of intervention content of the goal setting intervention (weeks 4-12) specified in terms of the Behavior Change Technique Taxonomy Version 1 and the Mode of Delivery Taxonomy.

BCT[a] and definition	Application in this study
Self-monitoring of behavior: establish a method for the person to monitor and record their behavior(s) as part of a behavior change strategy	Participant is provided with a Fitbit Alta activity tracker. Physical activity behavior is visually displayed on the screen, and a log of their previous activity is recorded and displayed on the app interface; MOD[b]: digital, wearable, and accessory; MOD: digital, phone, and app
Feedback on behavior: monitor and provide informative or evaluative feedback on performance of the behavior and must include one of form, frequency, duration, and intensity.	Once a week, the participant is contacted by SMS[c] text messages to inform them of their average daily step count; MOD: human, distance, and SMS text message
Goal setting (behavior): set or agree on a goal defined in terms of the behavior to be achieved	Participant is contacted by SMS text messages with a daily step count goal for the following week; MOD: human, distance, and SMS text message
Graded tasks: set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	The participants' step count goal is calculated by adding 10% to their previous week's average daily step count and sent by SMS text messages; MOD: human, distance, and SMS text message
Social reward: arrange verbal or nonverbal reward if and only if there has been effort and/or progress in performing the behavior (includes *positive reinforcement*)	The participant receives a congratulatory SMS text message if they successfully achieve their step count goal that week; MOD: human, distance, and SMS text message
Review behavior goal(s): review behavior goal(s) jointly with the person and consider modifying goal(s) or behavior change strategy in light of achievement	If the participant does not successfully achieve their step count goal, a new goal is calculated based on their previous week's activity level and sent by SMS text messages; MOD: human, distance, and SMS text message

[a]BCT: behavior change technique.

[b]MOD: mode of delivery.

[c]SMS: short message service.

Description

The intervention had 2 components: (1) a lifestyle information and education session delivered by health professionals (specifically, 3 physiotherapists, 1 dietician, and 1 clinical psychologist) at Letterkenny University Hospital and (2) goal setting intervention delivered by a behavioral science researcher using mobile technology.

Lifestyle Information and Educational Session (Week 1)

Participants in the intervention group attended a 1-day (4-hour) session in small groups of 10 to 15 people, where they received personalized and tailored lifestyle information from physiotherapists, a dietician, a clinical psychologist, and a behavioral scientist. Participants received a comprehensive presentation from each specialist. The physiotherapists demonstrated a series of daily strengthening exercises that were suitable and safe posttreatment. Moderate physical activity for 30 min 6 days a week, 45 min 4 days a week, or 10 min 2 times a day was recommended. Participants were advised to choose a personal activity schedule that best fit their lifestyle. Their preference or adherence to a particular schedule was not measured or controlled. The behavioral science researcher prescribed a weekly increase of 10% in average daily step count over the course of the program. The dietician advised participants to reduce their calorific intake, reduce red meat, processed meat, salt and sugar, and increase fruit, vegetable, and fiber intake. Participants were provided with an information sheet to take home summarizing the key messages from the lifestyle information and education session and booklets by the World Cancer Research Fund on healthy eating and physical activity. The BCTs included in this session are shown in Table 1.

Goal Setting Intervention (Weeks 4-12)

Participants in the intervention group self-monitored their physical activity using their Fitbit. In addition, participants in the intervention group were contacted by the behavior specialist through SMS text messages on weeks 4 to 11 to provide feedback on their average daily step count, review physical activity goals, and set graded tasks (increase daily step count by 10%). Participants gradually increased their physical activity (+10% each week) toward the recommended 10,000 steps per day. Participants continued to self-monitor their progress for the remaining 3 months of the study without review/feedback from the behavior specialist. The BCTs included in the goal setting intervention are presented in Table 2.

Materials

Each participant was provided with a Fitbit activity tracker and registered with a Fitbit user account. The Fitbit is an accelerometer-based device that is worn on the wrist. The intervention group wore the Fitbit Alta to track health outcomes. Summary data (eg, step count and active minutes) were visible on the device display, and additional data (eg, sleep data) were available on the Fitbit app dashboard.

Control Condition

Although the intervention was specifically designed to deliver key BCTs, a number of BCTs are present in standard medical care and therefore also present in the control condition in this study (summarized in Table 3).

Table 3. Description of control condition content specified in terms of the Behavior Change Technique Taxonomy Version 1 and the Mode of Delivery Taxonomy.

BCT[a] and definition	Application in this study
Goal setting (outcome): The person is encouraged to set a general goal that can be achieved by behavioral means but is not defined in terms of behavior (eg, to lose weight), as opposed to a goal based on changing behavior.	All participants enrolled in the research study are encouraged to lose weight by increasing their level of physical activity and improving their diet; MOD[b]: digital, wearable, and accessory
Provide information on consequences of behavior to the individual: information about the benefits and costs of action or inaction to the individual or tailored to a relevant group based on that individual's characteristics.	Participants in the control group attend a small group session to receive their Fitbit Flex 2. Standard advice regarding healthy diet and lifestyle is provided at this session; MOD: printed material and leaflets
Self-monitoring of behavior: establish a method for the person to monitor and record their behavior(s) as part of a behavior change strategy.	Participant is provided with a Fitbit Flex 2 activity tracker. The visual display does not provide summary data, the app interface is modified to not present summary data, and the participant is not given any method for monitoring/recording their activity level using Fitbit; MOD: digital, wearable, and accessory

[a]BCT: behavior change technique.

[b]MOD: mode of delivery.

Materials

All participants in the control group were provided with Fitbit Flex 2 to track health outcomes. The display panel on this device does not present summary data (ie, step count and number of active minutes), and the application dashboard was modified to not display summary data.

On being recruited to the study based on meeting the eligibility criteria (BMI ≥25 kg/m^2), all participants were encouraged to lose weight (ie, BCT; *goal setting [outcome]*) because of health care professionals' duty of care. Participants in the control group attended a 15-min session in small groups of 10 to 15 participants, where they received a Fitbit Flex 2. In addition, as in standard medical care, there was provision of health information at this session (ie, BCT *information on consequences of behavior to the individual*, but not BCT *instruction on how to perform the behavior* or *demonstration of the behavior*). Therefore, leaflets were made available, and standard advice was available from oncology nursing staff on request. No further information was given at this time. Finally, participants in the control group wore the Fitbit Flex 2 for monitoring their physical activity, but without *goal setting (behavior)*. The visual display on the device and the app limited but did not eliminate their ability to *self-monitor* behavior.

Participants

Inclusion Criteria

Adults aged 18 to 70 years, having a calculated BMI equal to or greater than 25 kg/m^2, with a solid cancer and who had completed cancer treatment (except for hormone therapy), attended Oncology Services in Letterkenny University Hospital during the recruitment phase, and had a willingness to use mobile technology were eligible to participate. A total of 10 eligible participants who did not own a smartphone were provided with an Amazon Fire 7 Tablet.

Recruitment and Consent

The clinical team identified 159 eligible participants who were identified sequentially from the oncology outpatient waiting list. The research team contacted them by telephone and described the aims and design of the study. Prospective participants who were interested in the study were sent an invitation letter, participant information sheet, and consent form. Informed written consent was provided by 123 participants (77.3% response rate) who attended baseline assessments. Participant characteristics are described in Table 4.

Of the 36 participants who did not consent to participate, 28 were not interested, 3 were waiting for surgery, 1 had chronic obstructive pulmonary disease, 1 was undergoing recurrence workup, 2 had young children, and 1 did not drive (see Figure 2).

Table 4. Participants' characteristics at baseline assessment.

Characteristics	Control	Intervention	2-tailed *t* test (*df*)	*P* value
Age, mean (SD)	59.24 (7.65)	55.61 (8.05)	2.39 (105)	.02
Weight (kg), mean (SD)	87.10 (16.32)	84.18 (13.98)	0.99 (105)	.32
BMI[a] (kg/m^2), mean (SD)	32.64 (5.41)	30.33 (3.99)	2.53 (105)	.01
Gender, female:male	49:4	42:12	—[b]	—
Have you ever been told by a doctor that you have or have had any of the following conditions?, n (%)				
Angina	1 (1.9)	2 (3.7)	—	—
Heart attack	3 (5.7)	1 (1.9)	—	—
High blood pressure	19 (35.8)	18 (33.3)	—	—
Stroke	3 (5.7)	1 (1.9)	—	—
Diabetes	5 (9.4)	6 (11.1)	—	—
High cholesterol	21 (39.6)	20 (37.0)	—	—
Depression	12 (22.6)	9 (16.7)	—	—
Anxiety	12 (22.6)	12 (22.2)	—	—

[a]BMI: body mass index.

[b]Not applicable.

Sample Size

The statistical program G*Power was used to conduct power analysis. With 2 groups (intervention and control), 3 measurements (baseline, time 1, and time 2), an assumed correlation among repeated measures of 0.3, and a small-medium effect size and a power of 0.8, the recommended sample size for repeated measures analysis of variance (ANOVA) was 102. Sample size calculations were made considering attrition rates (approximately 20%) observed in similar studies using mobile technology interventions with cancer survivors [24].

Procedure

A flow diagram of the progress through each phase of this 2-group parallel randomized trial is presented in Figure 2. A total of 123 eligible participants attended baseline assessments. Participants were randomized to the control or intervention arm. Of 123 participants, 62 assigned to the intervention group were invited to attend a lifestyle information and education session where they would also receive their Fitbit activity monitor, and 55 were able to attend. During the lifestyle information and education session, each participant was provided with a Fitbit Alta. The Fitbit activity tracker was set up and paired with the participants' mobile device. The participant was given an information sheet with instructions on how to synchronize their Fitbit device and app and asked to perform this weekly.

The remaining 61 participants assigned to the control group were invited to an appointment where they would be provided with a Fitbit activity monitor, and 53 were able to attend. During this meeting, each participant was provided with a Fitbit Flex 2. The Fitbit was paired with the participants' mobile device. The participant was given an information sheet with instructions on how to synchronize their Fitbit and asked to perform this weekly or at least once a month to prevent loss of data.

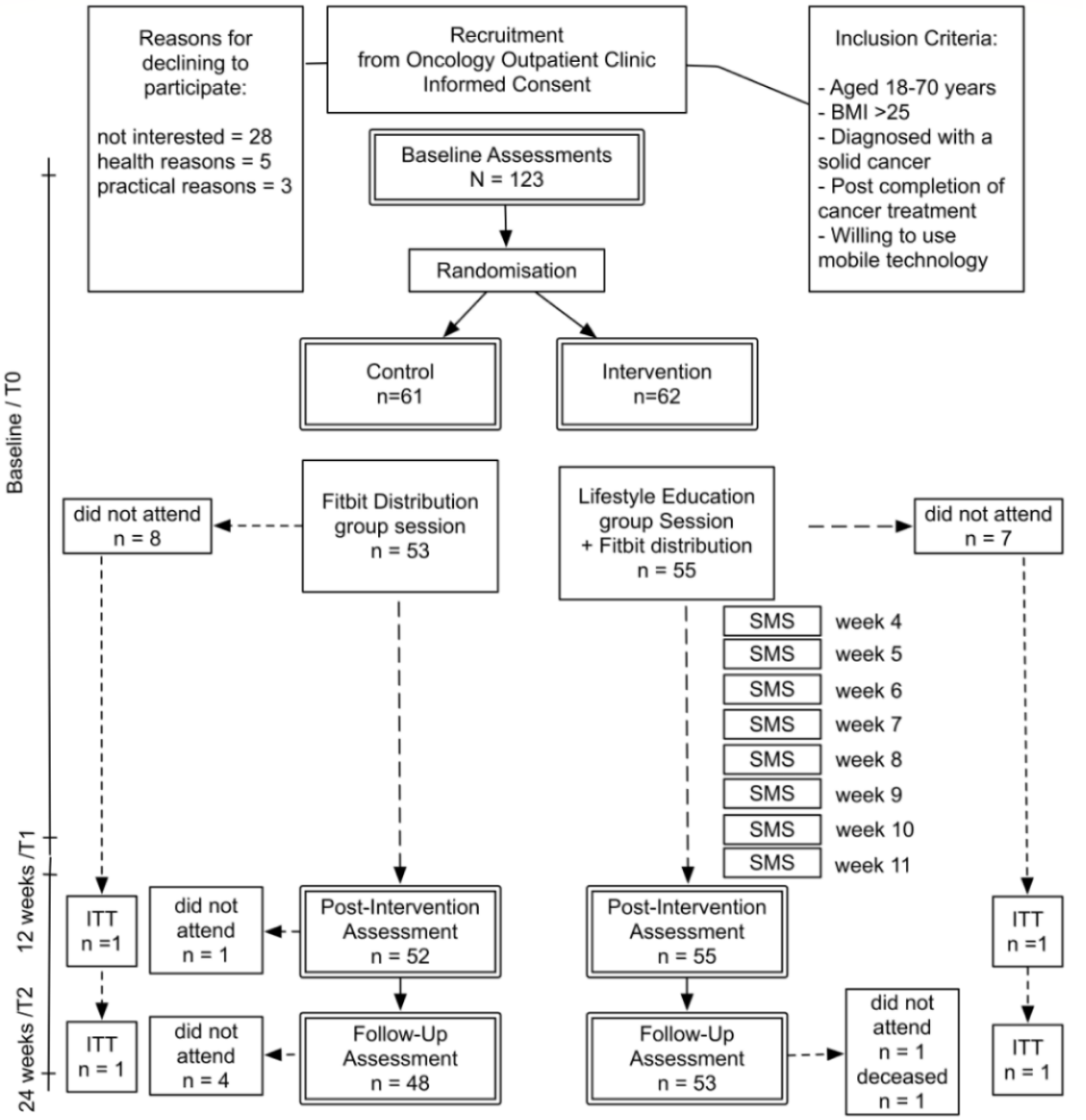
All participants wore a Fitbit® activity monitor for the 6-month duration of the study. Participants in the intervention group received weekly personalized SMS text messages, including feedback on their physical activity level and a personalized physical activity goal each week for 8 weeks.

All participants were invited to a postintervention assessment (12 weeks later) to determine efficacy of the lifestyle information and education session and personalized goal setting mHealth intervention for increasing physical activity and improving clinical and psychological outcomes.

All participants continued to wear Fitbit for the remainder of the study, but the personalized goal setting intervention had ceased after 12 weeks. To determine if any effects of a lifestyle information and education session and personalized goal setting mHealth intervention were maintained 3 months later, all participants were invited to a follow-up assessment (6 months after baseline assessment).

At the conclusion of the study, all participants in the intervention group were invited to be interviewed about their experience of the Moving On program, and 13 interviews were conducted.

Figure 2. Flow of participants through each stage of the current randomized controlled trial. BMI: body mass index; ITT: intention-to-treat; SMS: short message service.



Outcomes

The outcomes measured at baseline (T0), 12 weeks (T1; intervention ends), and 24 weeks (T2; follow-up) are described below.

Clinical Outcomes

Anthropometric Measurements

Weight was measured in light clothing without shoes in kilogram plus 2 decimal places using a calibrated Seca scale. Height was recorded without shoes in centimeters plus 2 decimal places using a stadiometer. BMI was calculated using weight and height. Waist circumference was measured at the halfway point between the hip bone and lowest rib using a stretch-resistant measuring tape [25]. To standardize measurement, one set of scales and stadiometer were used on all participants at each assessment.

Functional Exercise Capacity

The 6-min walk test is a clinical exercise test that measures the distance walked in 6 min on a hard, flat surface. Systolic blood pressure, diastolic blood pressure, heart rate, blood oxygen saturation, subjective fatigue, and dyspnea were measured pretest, posttest, and 4 min later.

Psychological Outcomes

Medical Outcomes Survey Short Form (RAND36) [26] is composed of 36 items, measuring 8 individual subscales that represent 3 general areas of health-related quality of life: physical, emotional, and social well-being. The subscales

include physical functioning, role function–physical (role limitations caused by physical factors), role function–emotional (role limitations caused by emotional factors), bodily pain, social functioning, emotional well-being, energy/fatigue, and perceived general health. Each subscale is standardized on a scale from 0 to 100, with higher scores indicating better functioning.

The Three-Item Loneliness Scale [27] consists of 3 questions such as "How often do you feel that you lack companionship?" The responses are coded 1: hardly ever, 2: some of the time, and 3: often. Scores range from 3 to 9, with higher scores indicating greater loneliness.

The Brief Fatigue Inventory [28] comprises 9 items measured on a 10-point Likert scale. The scale is composed of 2 subfactors that assess the severity of fatigue and its effects on the respondent's ability to perform activities of daily living. Scores range from 0 to 90. Higher scores represent worse self-reported fatigue.

The General Self-Efficacy Scale [29] is a 10-item measure with answers ranging from *not true at all* to *exactly true*. It assesses the participants' belief in their ability to succeed in certain situations. Scores range from 10 to 40, with higher scores indicating higher self-efficacy.

Exercise self-efficacy was assessed using a 4-item measure developed in a previous study by Armitage [30]. Items were as follows: "To what extent do you see yourself as being capable of participating in regular physical activity? incapable–capable"; "How confident are you that you will be able to participate in regular physical activity? not very confident–very confident"; "I believe I have the ability to participate in regular physical activity. definitely do not–definitely do"; and "How much personal control do you feel you have over participating in regular physical activity? no control–complete control. Items were measured using 7-point scales.

Social support for physical activity was measured using a 3-item measure developed by Molloy et al [31] that was based on an earlier measure [32]. The items began with the stem "In the last week I...had somebody to encourage me to participate in physical activity on a regular basis,...had somebody to participate in physical activity with me,...felt supported in having a regular pattern of physical activity." The responses to the 3 items were on a 7-point scale and ranged from 1: disagree to 7: agree.

Health Behavior Outcomes

Self-reported physical activity level was measured using the 4-item Godin Leisure-Time Exercise Questionnaire [33]. Respondents rate the frequency of 15-min bouts of strenuous, moderate, and mild exercise in a 7-day period. Participants also rate how often they engage in regular activity sufficient to break a sweat (1 often, 2 sometimes, and 3 never). Higher scores indicate higher subjective physical activity.

Objective physical activity level (ie, average daily step count) was measured continuously using the Fitbit activity tracker.

Dietary data were collected using the European Prospective Investigation into the Cancer and Nutrition (EPIC) Norfolk Food Frequency Questionnaire (FFQ) [34]. Participants were asked to report the frequency of 130 different foods and beverages consumed over the previous 3 months. The FFQ EPIC Tool for Analysis [35] provides estimates of 10 food groups.

Acceptability

A 5-item acceptability measure was created based on the topic guide for the semistructured interviews. The topic guide itself was informed by the theoretical framework of acceptability [22]. Using a 5-point Likert scale, participants in the intervention were asked to rate their satisfaction with the intervention (affective attitude), perceived effectiveness of the intervention, their confidence in performing the behaviors required to participate (self-efficacy), the perceived amount of effort required to participate (burden), and the extent to which they understand how the intervention is intended to work (coherence).

Statistical Analysis

To maximize power and conform to intention-to-treat analysis, missing data will be handled using multiple imputation methods (ie, the expectation-maximization algorithm) if assumptions regarding mechanisms of missingness are met.

A series of 3 (baseline, T1, and T2) × 2 (control and intervention) mixed ANOVAs will be performed to determine the efficacy of a lifestyle information and education session and goal setting mHealth intervention on clinical, psychological, and health behavior measures.

Independent sample *t*-tests will be used to analyze group differences (control and intervention) in average daily step count across the 24 weeks of the study.

Thematic analysis of interview transcripts will be used to explore the acceptability of the Moving On program for recipients.

Quantitative data will be analyzed with IBM SPSS Statistics 24. NVivo 12 will be used to facilitate organization and analysis of qualitative data.

Results

The recruitment for this study commenced in December 2017 and data collection began in January 2018. Data collection was completed by September 2018, and analysis is underway. Results are expected to be submitted for publication in winter 2019.

Discussion

This protocol describes an RCT designed to evaluate the efficacy of an intervention using mobile technology and BCTs to improve health and well-being outcomes in a sample of cancer survivors with a BMI of 25 kg/m^2 or greater. Strengths of the study protocol include a description of the intervention content in terms of a standardized list of BCTs [13] and the MOD taxonomy [23], as well as a description of control condition content using the same standardized descriptors. Qualitative elements examining the acceptability of the intervention are an additional strength of the study.

Cancer survivors require additional support to self-manage lifestyle behaviors. mHealth technology may provide a cost-effective solution within modern oncology care. However, there is limited evidence for the effectiveness of mHealth interventions for behavior change with cancer survivors. mHealth is a novel area of research, and although it holds enormous potential for improved health care delivery in the future, it currently lacks a strong evidence base [36]. This study evaluating the efficacy of an mHealth intervention using evidence-based BCTs to improve health and well-being outcomes in a sample of cancer survivors who are overweight represents an important contribution to the field. If results of the study find the *Moving On* program to be effective and acceptable to participants, possibilities for full-scale national roll-out will be explored.

The findings of this study will be of interest to health care professionals and patients, health psychologists with an interest in behavior change, and those developing new technologies to support health behavior change.

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Conflicts of Interest

None declared.

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Abbreviations

ANOVA: analysis of variance
BCT: behavior change technique
BCW: behavior change wheel
BMI: body mass index
EPIC: European Prospective Investigation into the Cancer and Nutrition
FFQ: Food Frequency Questionnaire
mHealth: mobile health
MOD: mode of delivery
RCT: randomized controlled trial
SMS: short message service

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Protocol

Radiofrequency-Assisted Liver Resection Versus Clamp-Crush Liver Resection: Protocol for an Updated Meta-Analysis and Systematic Review

Osman El-Koubani[1,2], BSc, MBBS; Mark McCann[2,3], MSc, MBChB; Daniel Christmas[1,2], BSc, MBBS; Aakash Khanna[1], BSc, MBBS; Alexander von Maydell[1], BSc, MBBS

[1]Faculty of Medicine, Imperial College London, London, United Kingdom

[2]Department of General Surgery, Royal Infirmary Edinburgh, Edinburgh, United Kingdom

[3]Faculty of Medicine, University of Aberdeen, Aberdeen, United Kingdom

Corresponding Author:
Osman El-Koubani, BSc, MBBS
Faculty of Medicine
Imperial College London
Exhibition Road
South Kensingston
London, SW7 2AZ
United Kingdom
Phone: 44 20 7589 5111 ext 1
Email: osman.el-koubani@nhs.net

Abstract

Background: Malignancy of the liver has historically meant a poor prognosis and remains the second most common cause of cancer-related deaths globally. Traditionally, hepatectomy has utilized the clamp-crush technique; however, this is associated with high incidence of postoperative complications. Many novel techniques have been developed—radiofrequency ablation and transarterial chemoembolization; however, these are not applicable to numerous cases. Clamp-crush liver resection (CCLR) remains the gold standard. Radiofrequency-assisted liver resection (RFLR) is a technique that aims to reduce mortality through bloodless liver resection. A systematic review was previously performed on RFLR but the results neither recommended nor refuted the use of RFLR owing to the lack of sufficient evidence from well-designed randomized controlled trials (RCTs) at the time.

Objective: The aim of the study is the meta-analysis and systematic review of recent studies comparing RFLR against CCLR.

Methods: Articles comparing RFLR and CCLR that were published from 2014 until 2019 will be reviewed and relevant data will be extracted and statistically analyzed through Review Manager 5 (by the Cochrane Collaboration) together with the results of the previous meta-analysis.

Results: Data collection is currently underway, with papers being screened. We hope to publish the results by the end of 2019.

Conclusions: Given the high mortality rates currently associated with liver resection, it is imperative that novel surgical techniques are undertaken and investigated so we can improve best practice guidance and outcomes.

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KEYWORDS

radiofrequency; hepatectomy; systematic review; meta-analysis

Introduction

Background

Malignancy of the liver has historically meant a poor prognosis for patients and remains the second most common cause of cancer-related deaths globally [1]. Many novel nonsurgical techniques for treating carcinoma of the liver have been developed, such as radiofrequency ablation or transarterial chemoembolization [2]. These techniques have shown promising results in their early usage. However, liver resection continues to be the primary intervention for management of benign and malignant liver lesions. Although advancements in techniques for resection have led to better morbidity and long-and-short-term mortality rates in recent years, only a few patients remain eligible for surgery, given the risks associated with surgery. Concerns regarding surgery are primarily related to intraoperative bleeding time and subsequent requirement of blood transfusion, both of which have been shown to lead to poor outcomes [3,4]. The risks associated with bleeding are especially pertinent as many patients with liver tumors have concurrent poor liver function.

Incidence of hepatocellular carcinoma (HCC) is predicted to rise to 22 million over the next few decades owing to rises in cirrhotic liver disease related to alcohol and viral hepatitis and Noncirrhotic Liver Disease related to Fatty Liver Disease [5]. Given these projections, further innovation in management of liver tumors is necessary to continue improving outcomes and access to treatment for patients. Standard methods for liver resection traditionally utilize the clamp-crush technique, which allows for parenchymal transection of the liver with reduced bleeding intraoperatively. The Pringle maneuver is commonly employed during liver surgery, which clamps the hepatoduodenal ligament, thus interrupting blood flow through the hepatic artery and portal vein. It does however often result in the risks previously specified such as bleeding, requirement for transfusion, and leaking of bile postoperatively, all of which affect mortality and morbidity. Patients with poor hepatic reserve are also at risk of hepatic reperfusion injury owing to occlusion of blood flow.

Recent advances in surgical technology have led to the development of devices utilizing radiofrequency. These devices do not require hilar dissection or blood flow occlusion, mitigating risks associated with blood loss and reperfusion injury. The devices coagulate viable tissue around the resection margin, allowing for subsequent excision with minimal blood loss. A meta-analysis in 2014 by Xiao et al [6] looked at 9 studies showing statistically significant reduction in intraoperative blood loss in patients when comparing radiofrequency-assisted liver resection (RFLR) with clamp-crush liver resection (CCLR). There was, however, no significant difference observed in requirements for blood transfusion and showed increased rates of bile leak and intra-abdominal abscess [6]. Therefore, Xiao et al [6] concluded that the evidence neither supported nor refuted the use of RFLR. Since this study, multiple additional studies comparing RFLR and CCLR have been published. One recent meta-analysis conducted by Reccia et al in 2017 [7] was specifically interested in laparoscopic radiofrequency liver resections. They concluded that this type of resection was a safe and feasible procedure for both benign and malignant liver disease associated with a reduction in blood loss and hospital mortality rate [7]. Laparoscopic RFLR, however, constitutes a small minority of laparoscopic liver resections [7], which itself is not standard treatment for patients with localized colorectal metastases or HCC [8]. This meta-analysis is therefore interested in assessing the efficacy of open RFLR against CCLR, which would be more representative of common practice. There is still no definitive work arguing in favor or against the use of RFLR; therefore, we are unable to design guidance on best practices with regard to liver resection. Given the potential benefit of bloodless liver resection, this meta-analysis will be undertaken to give an update on developments by including the most recent studies.

Approach

A systematic review will be undertaken assessing the recent studies from 2014 until 2019 that compare RFLR with CCLR for all various types of devices that utilize radiofrequency energy for liver resection. The search strategy will therefore include any individual device that has evidence published comparing its efficacy to CCLR, such as Habib 4X System, Cool-tip System, Tissue Link, and Radionics. Relevant data from these studies and the meta-analysis by Xiao et al [6] will be extracted and a combined meta-analysis will be performed.

Objectives

Population, Intervention, Comparison, and Outcome Framework

- Population: patients requiring liver resection for benign or malignant liver disease in both normal and cirrhosed liver.
- Intervention: RFLR.
- Comparison: CCLR.

Outcome Measure

- Primary outcome: intraoperative blood loss.
- Secondary outcomes: (1) operation time; (2) number of patients developing postoperative bile leak; (3) number of patients requiring blood transfusion; (4) number of patients developing intra-abdominal abscess; and (5) mortality at 30 days.
- Study design: all human study types (randomized and nonrandomized) comparing RFLR and CCLRs.

Methods

The source databases were as follows: (1) PubMed (2) Ovid (3) EMBASE and (4) Cochrane.

Search Strategy

Mirroring the search strategy employed by Xiao et al [6], we will search in the fields of *Abstract* and *Title* radiofrequency together with *hepatectomy, liver resection, liver transection*, or *liver surgery* as keywords, in addition to using the medical subject headings term *hepatectomy* with subheading *mortality*. The search will begin from December 2012, the date which represents when the previous systematic review by Xiao et al

was performed [6]. No upper date limit will be used. There will be no language restrictions for the search.

Search String

(((radiofrequency[All Fields] AND "hepatectomy/mortality"[Mesh Terms]) OR (radiofrequency[All Fields] AND liver resection[Title/Abstract])) OR (radiofrequency[All Fields] AND liver transection[Title/Abstract])) OR (radiofrequency[All Fields] AND liver surgery[Title/Abstract]) AND ("2012/12/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms]

Eligibility

Inclusion Criteria

The inclusion criteria were as follows: all studies published as full-text articles from peer-review journals comparing RFLR and CCLR in which at least data from one of the quantitative outcomes mentioned are reported. These studies had to have more than 20 patients included in them.

Exclusion Criteria

1. Nonhuman studies.
2. No control group.
3. Publication not available in English.
4. Review articles.
5. Letters and editorial comments.
6. Case reports.

Screening

We will use the Systematic Review Facility Web-based screening tool to screen the title and abstract of each paper that is identified in our literature search. This will be done by 2 independent reviewers (EO and MM) assessing each paper's eligibility against our inclusion and exclusion criteria. A third reviewer (CD) will then confirm the appropriateness of extracted papers.

Quality Assessments

Quality assessment will mirror similar methodologies to Xiao et al [6] to accurately compare the quality of all studies. Randomized controlled trials (RCTs) and nonrandomized studies will be assessed as shown below.

Randomized Control Trials

The quality of all RCTs will be assessed using a modified Jadad score, comprising the following 5 variables [9]:

1. Randomization.
2. Generation of random numbers.
3. Details of the double-blinding procedure.
4. Information on withdrawals.
5. Concealment of allocation.

One point is allocation for each variable from the criteria that a study includes, totaling a maximum score of 5.

Nonrandomized Controlled Trials

The quality of all non-RCTs will be assessed using the modified Newcastle-Ottawa scale that is recommended by the Cochrane Collaboration [10], comprising the following 3 variables [11]:

1. Patient selection—comprising 4 items, worth one point each.
2. Comparability of study groups—comprising 1 item, worth up to 2 points.
3. Assessment of outcomes—comprising 3 items, worth one point each.

Therefore, the maximum score is 9, and the score is represented by stars. Studies labeled with 6 or more stars will be considered to be of high quality.

Statistical Analysis

Analysis of the data will be done through Review Manager 5, provided by the Cochrane Collaboration. All included studies for each outcome measure will be presented graphically and plotted on a forest plot. The comparison of dichotomous outcomes will be through their odds ratios with 95% Cis. Continuous variables will be compared through their weighted mean differences with 95% CI. Any *P* value <.05 will be deemed statistically significant. Heterogeneity will be assessed using I^2 values. Low heterogeneity will be defined as an I^2 value of 50% or less, in which case the fixed-effects model will be used. If there is high heterogeneity between studies, the random-effects model will be implemented. To identify patient groups that may benefit from this treatment, for example, patients with cirrhotic livers, a subgroup analysis will also be undertaken for more homogeneous studies.

Results

Data collection is currently underway, with the screening process being undertaken. We will then begin data analysis, with the expectation to publish results and a full manuscript by the end of 2019.

Discussion

Given the growing complexity of patients, a procedure that reduces the known risks associated with high morbidity and mortality is desirable. Although intraoperative blood loss and subsequent blood transfusions are traditionally expected within surgery, in relation to liver resection, it is associated with poor outcomes. The crucial period in minimizing blood loss is during division of the liver parenchyma. Surgical techniques such as radiofrequency can theoretically eradicate bleeding during this period, leading to bloodless liver resections, thus improving outcomes for patients. However, if new surgical techniques such as RFLR cause a rise in postoperative complication rates, for example, bile leak and infection, they will not be favorable alternatives to traditional CCLR. Given the poor outcomes currently associated with liver resection, it is imperative that new best practice surgical techniques are undertaken.

Conflicts of Interest

None declared.

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Abbreviations

CCLR: clamp-crush liver resection
HCC: hepatocellular carcinoma
RCT: randomized controlled trials
RFLR: radiofrequency-assisted liver resection

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Proposal

Assessing the Content Validity of a New Patient-Reported Measure of Barriers to Antiretroviral Therapy Adherence for Electronic Administration in Routine HIV Care: Proposal for a Web-Based Delphi Study

Kim Engler[1], PhD; Sara Ahmed[1,2,3], PhD; David Lessard[1], PhD; Serge Vicente[4], MSc; Bertrand Lebouché[1,5,6], PhD, MD

[1]Center for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

[2]School of Physical & Occupational Therapy, McGill University, Montreal, QC, Canada

[3]Centre de recherche interdisciplinaire en réadaptation (CRIR), Constance Lethbridge Rehabilitation Center, Montreal, QC, Canada

[4]Department of Mathematics and Statistics, University of Montreal, Montreal, QC, Canada

[5]Department of Family Medicine, McGill University, Montreal, QC, Canada

[6]Chronic Viral Illness Service, Royal Victoria Hospital, Montreal, QC, Canada

Corresponding Author:
Kim Engler, PhD
Center for Outcomes Research and Evaluation
Research Institute of the McGill University Health Centre
5252 de Maisonneuve Blvd
Montreal, QC, H4A 3S5
Canada
Phone: 1 514 934 1934 ext 32126
Fax: 1 514 843 2207
Email: kimcengler@gmail.com

Abstract

Background: Adherence to lifesaving antiretroviral therapy (ART) for HIV infection remains a challenge for many patients. Routine screening for barriers to ART adherence could help make HIV care more patient-centered and prevent virologic rebound or failure. Our team is currently developing a new HIV-specific patient-reported outcome measure (PROM) of these barriers for use in Canada and France along with a digital app for its electronic administration. In our previous work, we developed the PROM's multidimensional conceptual framework and generated 100 English items, which have been translated to French.

Objective: This study aims to use a Web-based Delphi to help validate and select the content of this new HIV-specific PROM, based on the perspective of anglophone and francophone patients and providers in Canada and France. Here, we present the proposal for this Delphi.

Methods: This modified Delphi will involve a diverse panel of patients (n=32) and providers (n=52) recruited especially from the 9 sites of the PROM development study (site locations in Canada: Montreal, Toronto, Vancouver; in France: Paris, Nantes, Clermont-Ferrand, Saint-Martin, Cayenne). Overall, 2 rounds of Web-based questionnaires will be conducted. The threshold for consensus is set at 60% and will determine which items are carried forward to the second round. Per item, 3 aspects will be rated: importance as a barrier to ART adherence, relevance for HIV care, and clarity. In both rounds, space will be available for free text comments. Overall comprehensiveness will be assessed in the second round.

Results: This study has undergone a methodological review by experts in patient-oriented research. It has received approval from a research ethics board of the McGill University Health Centre. It is financially supported, in part, by the Canadian Institutes of Health Research's Strategy for Patient-Oriented Research-Quebec Support Unit (M006). As of May 21, 2019, 15 people living with HIV and 25 providers completed the first round of the Delphi (24 from Canada and 16 from France).

Conclusions: To our knowledge, this is the first Delphi to seek consensus on the most relevant and clinically actionable barriers to ART adherence, collecting opinions on an extensive list of barriers. Drawing on a relatively large and diverse panel of HIV patients and providers, it essentially engages key stakeholders in decision making about the PROM's final content, helping to ensure its utility and adoption.

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KEYWORDS

HIV; antiretroviral therapy, highly active; patient-reported outcome measure; medication adherence; Delphi technique; stakeholder participation; Canada; France

Introduction

Rationale for the New Measure

The success of antiretroviral therapy (ART) for the treatment of HIV currently depends on adequate daily adherence to suppress replication of the virus. Both people living with HIV (PLHIV) and providers agree that adherence is among the top priority areas of HIV clinical care [1]. As a wide variety of factors can impede it [2], it remains a challenge for many. Approximately 40% of adult PLHIV on ART in North America and western Europe are estimated to be less than 90% adherent [3], and, thus, do not attain ideal levels of adherence. In HIV care, clinical guidelines recommend regularly identifying patients' barriers to ART adherence [4]. However, without a tool for this purpose, a thorough in-clinic assessment may not occur. It could be hindered, for instance, by its potentially time-consuming nature [5], poor quality communication about ART adherence [6,7], or inaccurate estimation of patient adherence [8,9]. Systematically using an electronically administered patient-reported measure for this purpose could provide a relatively quick and affordable solution, offer opportunities for patient-centered counseling and intervention [5], and help prevent virologic rebound (plasma HIV ribonucleic acid (RNA) levels >200 copies/mL, following suppression of the virus) or failure (persistent HIV RNA at these levels) [4]. Yet, no extant measure of barriers to ART adherence appears to have been designed for this purpose or to be sufficiently comprehensive (Engler et al, in press). Hence, our research team is currently developing a new patient-reported outcome measure (PROM) for use in HIV care in Canada and France that will be accessible through a digital app. This electronic PROM (e-PROM) will help to routinely detect and monitor an extensive range of barriers to ART adherence. PROMs are instruments or tools that directly assess, from the patient's perspective, their health, quality of life, or functional status associated with their health care or treatment [10]. Our preliminary work has led to the generation of a conceptual framework for the measure, which specifies multiple barrier domains for consideration and based upon which measure items were drafted. The latest version of the framework is presented in Figure 1.

Figure 1. The patient-reported outcome measure's conceptual framework of barriers to antiretroviral therapy adherence (revised from Engler et al, 2018, following the item generation and translation processes). ART: antiretroviral therapy.

Origin of the Measure's Conceptual Domains and Items

When developing a PROM, it is important to measure domains that are relevant to the target patients [11], in this case, PLHIV on ART. We therefore derived the domains from a synthesis of the results of 41 qualitative studies on ART adherence barriers among ART-experienced PLHIV in developed countries [12]. All included studies were published in the combination ART era, which began in 1996 (range: 1999 to 2015), with over half published from 2006 [12], when single-tablet regimens were introduced. The 6 broad domains of the conceptual framework arising from this study closely correspond with the dimensions of the World Health Organization's model of adherence across chronic conditions [13]. The framework also has 20 distinct subdomains, which were submitted to the patient advisory committee of our PROM development study for input [12]. Relevance ratings on all subdomains indicated either unanimous relevance or top-5 priority status for 12 subdomains, with mixed ratings on the others.

From these subdomains, 100 English items were drafted, virtually all referring to a specific barrier mentioned in at least 4 (10%) of the studies included in the synthesis [12]. On the basis of recommendations for measure development to consider existing items [14], the content of well over 100 PROMs (HIV-specific and generic) of related concepts was examined for candidate items. Many examined measures can be found in our reviews of HIV-specific PROMs (Engler et al, in press; [15]). Few extant items were integrated into the draft measure verbatim. Most generated items were inspired or adapted from items within the considered measures. Items were reviewed by our research team and then checked and revised for readability with: (1) the Question Understanding Aid (University of Memphis), a free software tool available over the Web; 2) scores generated by Microsoft® Word on Flesch Reading Ease (70.1) and the Flesch-Kincaid Grade Level (6.4), indicating *fairly easy* and Grade 6 level readability, as recommended [14]; and 3) a 2-hour pilot cognitive interview with a PLHIV in Montreal.

Following guidelines for the translation and cultural adaptation of PROMs [16], we produced a French version of the questionnaire, with the help of FACIT Translation Services. In short, the English items underwent 2 forward translations by native French speakers from Canada and France, reconciliation by our research team, 2 back-translations by native English speakers fluent in French, and review and finalization by our research team. The questionnaire was also formatted and proofread by 2 translators. The proof readings were then reconciled. This process generated both English and *universal*

(Canada-France) French versions of our PROM for further validation.

The French version of the PROM was not subjected to readability testing equivalent to that performed on the English version, before translation. However, readability was considered in the translation process. We also expect the Delphi and subsequent steps in our measure's development (eg, cognitive interviews in both Canada and France) to allow further checks on the items' readability.

The Need for Additional Stakeholder Engagement

When considering PROM use in clinical care, it is important to consult both patients and providers [17]. In such contexts, PROM utility and adoption is associated with how *relevant, meaningful, and actionable* scores are to end users [18]. Actionability refers to the utility of the information provided for clinical decision making. Specifically, PROM scores are actionable if providers know how to translate them into concrete actions (eg, treatment adjustment and referral) [19]. Furthermore, in developing a new PROM, evidence must be generated of its content validity, which refers to the relevance, comprehensibility, and comprehensiveness of its content for a specified construct, population, and use [20]. Other standards in PROM development include consideration of user burden (eg, length) [21]. Pragmatically, in the context of busy outpatient settings, shorter PROMs may be preferable [19], for example, to limit interruptions to clinic flow. Although we have an active Montreal-based HIV patient advisory committee [22] and have conducted qualitative needs assessments with HIV clinicians in France and Canada, in the planning of our new measure and its digital app [23], further stakeholder engagement was deemed necessary to respond to the above issues.

Study Objectives

The general objective of this study is to use a Web-based Delphi to help validate and select the content of a new HIV-specific PROM, based on the perspective of patients and providers in Canada and France. Specific objectives are to evaluate the relevance, actionability, comprehensibility, comprehensiveness, and crosscultural equivalence of the instrument's items (eg, French-Canada vs French-France).

Here, we outline the proposal for this Delphi.

Research Questions

The main research questions addressed and, in parentheses, the type of evidence to be examined are as follows. In the stakeholders' experience: (1) What items reflect important barriers to ART adherence? (relevance and crosscultural equivalence), (2) What items are relevant to HIV care? that is provide useful information for medical decision making (relevance, actionability, and crosscultural equivalence), (3) Are the items clear? (comprehensibility), and (4) Do the items address all relevant barriers? (comprehensiveness).

Methods

The Design

The proposed study will employ Delphi survey techniques, which are consensus-building methods [24]. More specifically, a Delphi involves group facilitation to obtain opinion consensus among a panel of *experts* through several rounds of anonymously completed questionnaires [24]. The questionnaire results are summarized and returned to the participants, following each round, and structure the next round's questionnaire [24]. This offers opportunities to panelists to change their responses, considering the group's collective opinion. The process typically ends when consensus is achieved or returns diminish.

A Delphi is a useful and recognized method for ensuring the content validity of new measures [25], as this type of validity relies on the judgment of experts [14]. As we will especially request that participants react to previously prepared material (ie, the new measure's items), our study design can be considered a *reactive Delphi* [26]. In avoiding a first round of open-ended questions, characteristic of a classical Delphi, it classifies as a modified Delphi [27].

The Panel

The panel will contain 2 broad stakeholder groups, HIV patients and providers, acknowledging potential differences in opinion [28]. The perspectives of HIV patients and providers can diverge on critical aspects of HIV care [1,29], on the preferred attributes of ART [30] and on whether adherence problems are present [8]. What factors are reported to contribute to the success or failure of electronic health interventions are also found to differ between patients (eg, patient empowerment and self-management) and providers (eg, health care quality and workflow) [31]. Hence, the groups may disagree on the aspects examined.

Sampling and Recruitment

Sample Size

Although variable, Delphi sample sizes of 15 to 20 participants are common [32]. With disparate or heterogeneous groups, larger samples may be required [33]. Nevertheless, in exercises involving expert content validation of a new measure, a panel of 8 to 12 experts can be considered large [34]. Given Cosmin standards for the sample sizes of quantitative content validity studies [20] and our budgetary limitations (see section on compensation), we decided to recruit 52 HIV health care, social and community service providers (ie, 12 each of physicians, nurses, and pharmacists; 5 each of social workers and psychologists or psychiatrists; 6 staff members of community-based organizations (CBOs); and 32 ART-experienced HIV patients. For Cosmin, 30 to 49 participants per group is deemed *adequate*, whereas 50 or greater is considered *very good*, the highest possible rating [20]. Half of the panel will be recruited from each country (Canada and France).

Inclusion Criteria

A Delphi is usually conducted with panelists who possess subject matter expertise on the given topic [25]. Sampling will thus be purposeful [35]. *Expertise* among HIV providers is arbitrarily defined as having at least 5 years of clinical practice experience with HIV patients. Among HIV patients, *expertise* is required in taking ART to control HIV infection and facing barriers to its use. HIV-positive persons will be eligible if they are aged at least 18 years, have been prescribed ART for at least 1 year, irrespective of current use of ART, and if, based on self-report, in the past 5 years, they had difficulty adhering to ART, as prescribed. This will help ensure that participants are knowledgeable of barriers to adhering to *current* ART regimens. Participants will need to confirm their easy access to the internet and comfort completing Web-based questionnaires in either English or French.

Recruitment

HIV providers will mainly be recruited within the 9 participating sites of the PROM development study in Canada and France, which is described elsewhere [22]. Patients will mainly be recruited by referral from providers at the participating clinics or through community organizations within the clinics' cities (in Canada: Montreal, Toronto, and Vancouver; in France: Paris, Nantes, Clermont-Ferrand, Saint-Martin, and Cayenne). Patient participants in Canada will be administratively included through the main study site, the Chronic Viral Illness Service of the McGill University Health Centre in Montreal, Quebec. At least 25% of participants recruited for each panel will be cisgender women, to ensure their equitable inclusion [36]. This lower limit is close to the estimated average proportion of PLHIV who are women in Canada (23% [37]) and France (32% [38]). At least 50% of providers and patients recruited in Canada will be fluent in English to allow adequate evaluation of each language version of the measure. A range of HIV providers that intervene on matters of adherence will be sought. Per country, we will recruit 6 clinicians, 6 pharmacists, 6 nurses, 2 to 3 social workers, 2 to 3 psychologists or psychiatrists, and 3 staff members of CBOs. Representation of at least 3 Canadian cities and 3 cities or collectivities in France will be sought for both patients and providers.

Gatekeepers will help identify eligible HIV providers [24] (eg, directors of the participating sites' HIV services and actors within the pharmaceutical industry). Emails will be sent to candidates within each site inviting them to participate in the Delphi. Those who accept will be directed to a secure website where they will be guided through the consent process [39].

In the participating sites, HIV patients will be approached by health care providers or research staff and referred to a designated staff member, if interested in the study. Eligibility and adequate inclusion of women will be verified among those who wish to participate. As with providers, eligible individuals, who accept, will be directed to a secure website where they will be guided through the consent process [39].

Delphi Procedure

The planned Delphi structure will involve only 2 rounds of data collection with Web-based questionnaires to limit costs, respondent burden, and attrition. To develop all participant questionnaires and acquire informed consent, we will use the SurveyMonkey software (SurveyMonkey Inc, San Mateo, California, USA). Before its use, the round 1 questionnaire, available in French or English, will be piloted with at least 2 clinicians and 2 patients. Once an individual has accepted to participate, has consented, and completed a brief survey on their characteristics, they may begin the Delphi's first round, which involves completing the associated questionnaire within 2 weeks. Within 2 weeks of receiving the panel's full data, feedback will be given to the panelists in the form of a report, detailing areas of consensus and disagreement. Any specific instructions for round 2 will be sent with the round 1 report, requesting panelist responses, again, within 2 weeks. Within 2 weeks of receiving round 2's data, a second report will be provided to panelists, describing the final results.

Reminders

Although ultimately under participant control, maintaining involvement is important to a Delphi's rigor and reminders can be used to enhance response rates [24]. A reminder will be sent to participants 1 week before the official deadline for completing the Web-based questionnaires. If necessary, up to 2 additional weekly reminders will be sent, if no data are received. Participants will be *asked* to complete the questionnaire within 2 weeks, but we will accord them a maximum of 4 weeks before considering them lost to follow up.

Measures to Ensure Anonymity

We will ensure the anonymity of panelists to each other but not to members of the research team. This *quasianonymity* is necessary to ensure follow-up of nonresponding participants [24] and to provide compensation for completed rounds. Standard measures to ensure research participant confidentiality will be in place.

Compensation

Attrition is particularly concerning in Delphi studies, because of their multiple rounds [27]. Delphi studies with HIV providers can document decreases in response rates from the first to the second round, from 33% to 0% (33% [1]; 20% [40]; 0% [39]). A decrease of 46% was reported in a recent Delphi study with HIV patients [41]. To foster retention, participants will be compensated for each completed Delphi round upon receipt and verification of their Web-based questionnaire data. Compensations set correspond to acceptable levels, as judged by the research ethics board (REB) that evaluated the study. PLHIV and community organization staff will be compensated the equivalent of $50 Canadian per round. Health and social service professionals will receive the equivalent of $100 Canadian per round. The differential is partially explained by ethical concerns about undue inducement of patients and the felt need to sufficiently incentivize professionals to ensure their participation. At consent, participants will also indicate if they wish to be acknowledged in any study or presentation arising from the Delphi results, provided they complete both rounds.

Instructions

Following the Web-based consent process, both patients and providers will complete a brief survey to allow description of

the panel. Both groups will provide information on their sociodemographic characteristics, whereas providers will answer additional questions on their HIV clinical practice and patients, on their HIV treatment (eg, whether currently on ART). For both Delphi rounds, patients and providers will complete identical Web-based questionnaires and receive instructions in simple language.

Round 1

Round 1 will be the most intensive for participants. The respondents' tasks will be, for each item proposed, to rate its (1) importance as a barrier to ART adherence (ie, Is this an important barrier to properly taking ART?), (2) relevance for HIV care (ie, Is this useful information for HIV care?), and (3) clarity (ie, Is the item clearly written? Does it make sense?). They will also provide comments, as needed (eg, suggested corrections and new items). For the list of items evaluated, contact the corresponding author.

Round 2

After considering the feedback provided in the round 1 report, respondents' main tasks for round 2 will be to review and rate the contested items on 1 to all of the same 3 aspects: (1) importance as a barrier, (2) relevance for HIV care, and (3) clarity (following item modification, if applicable). The measure's overall comprehensiveness will also be rated as will be any respondent-proposed items, if included.

Response Options

Relevance and importance will be measured with a slightly adapted frequently used four-point ordinal scale, appropriate for this purpose [34]: (1) No, (2) Somewhat, (3) Quite, and (4) Very. For simplicity, the same response scale will be used for item clarity and measure comprehensiveness. For each item, space for free text comments will be provided. Table 1 illustrates the question and response structure for each item evaluated at round 1. These will be modified for round 2, including only scales for an item's contested aspect(s).

Table 1. Responses collected for each patient-reported outcome measure item during round 1 of the Delphi.

Item	Answers			
Is this item...				
an important barrier?	No	Somewhat	Quite	Very
relevant for HIV care?	No	Somewhat	Quite	Very
clear?	No	Somewhat	Quite	Very
Comments (optional):				

Analyses

Determining Consensus

In the absence of standards for determining consensus in Delphi studies [43], our criterion was chosen to foster inclusivity and recognition of each stakeholder group's respective interests. As the measure contains items that are *causal indicators*, that is, they define the construct (ART adherence barriers) rather than being defined by it [14], inclusivity was doubly important. Exclusion of such items could lead to the underestimation of ART adherence barriers [14]. However, a 100-item measure seems impractical for routine use in HIV care.

For these reasons, we determined *a priori* that *consensus* on an item would be achieved if *60% or more* of either group (ie, 60% among patients or providers) or within the panel (ie, 60% of all participants) agree (ie, on importance, relevance, or clarity). In total, 60% is within the range of suggested proportions for determining consensus [26].

For example, if at least 60% of one group or of all participants agree that an item is important (ie, a score of 3 or 4 on the 4-point rating scale), consensus will be considered reached, as for relevance. For clarity, if minimum 60% of at least one stakeholder group or of all participants agree an item is not or only *somewhat* clear (ie, a score of 1 or 2), it will be reformulated and carried forward into round 2.

Items demonstrating consensus on importance and relevance, without clarity problems (as defined above), will not be carried forward into round 2. Any remaining items not meeting this condition after round 2 will be reevaluated. Specifically, given the complexity of the results generated by this Delphi and the panel's diversity, a multidisciplinary committee formed of investigators, providers, patients, psychometricians, and other experts will be constituted to review the final Delphi results and many potentially relevant comparisons (eg, by country and sex). The committee will make decisions about item removal or inclusion for the PROM and about which results to prioritize in the process.

Evaluating Content Validity

Consensus, as defined earlier, will determine the inclusion or exclusion of questionnaire items in round 2. However, for informative purposes, the content validity of each item will be calculated with the item-content validity index (I-CVI) [34]. This index will represent the proportion of experts in agreement about relevance and importance (ie, the number of experts scoring 3 or 4, divided by the total number of experts). As suggested by Polit et al [34], items with an I-CVI score of .78 or above will be considered to have an excellent content validity. This assessment of content validity will take account of I-CVI score comparisons across groups (eg, patients vs providers) and be considered by the multidisciplinary committee.

Exploring Crosscultural Equivalence

Crosscultural equivalence will be examined based on *item equivalence*, which concerns the relevance of items to the target population [14]. We will, therefore, compare the final I-CVI

item relevance and importance scores of anglophones with those of francophones and compare the scores of both francophone respondent groups (Canada vs France). This exercise will be exploratory; equivalence (eg, conceptual and measurement) will be further investigated in subsequent steps of the PROM development study (eg, with cognitive interviews and psychometric validation).

Descriptive Statistics

At each round, proportions endorsing each response option and measures of central tendency will be calculated (ie, medians and modes) [42], for all aspects considered.

Comparative Analyses

For descriptive purposes, statistical analyses of group comparisons (eg, patients vs providers) with nonparametric tests, appropriate with ordinal data (eg, Chi square and Fisher exact test with dichotomized variables) [43], will be conducted and shared with the participants. Tests of the stability of opinions on contested items from rounds 1 to 2 will also be performed (eg, with Wilcoxon matched-pairs signed-ranks test) [43].

Qualitative Analysis

If respondents provide sufficient written comments, they will be submitted to content analysis [44] to inform the interpretation of results.

Adding New Items

If new items are suggested at round 1 in the comments, they will be compared with the existing items and discussed by the research team to decide if they should be evaluated by panelists in round 2.

Feedback at Each Round

In line with recommendations and to stimulate consensus [42] and motivation, after a round, each participant will be given a report showing how their scores relate to the global results. Results will be presented for the full panel and stratified by general stakeholder group (patients, providers). A selection of all analyses conducted will be included in the report, to not overburden participants with information.

Results

Scientific and Ethics Reviews

This Delphi received methodological review by the Canadian Institutes of Health Research (CIHR), Strategy for Patient-Oriented Research (SPOR)-Quebec Support Unit, between March and May 2018, from Delphi experts on the Method Development team. The McGill University Health Center REB evaluated it as an amendment to the previously approved e-PROM development study. It granted approval on November 30, 2018.

Stakeholder Feedback on the Study and Contributions to Date

In November 2018, the Delphi Study was presented for feedback to our Montreal-based Knowledge Users Committee, which includes a strong representation of CBOs. As a result, it was decided to include CBO staff on the expert panel. In December 2018, the round 1 questionnaire was piloted in Montreal with 2 providers (a francophone pharmacist and an anglophone nurse) and 2 female patients (1 francophone and 1 anglophone), leading to more specific instructions to patients. To help limit the impact of computer literacy and internet access on patient participation, in partnership with a CBO, AIDS Community Care Montreal, a computer workshop and terminals were available to potential participants, leading to the inclusion of 5 participants in April 2018. There are also plans through our partnership with this CBO to include an incarcerated individual who would complete the questionnaire on paper.

Recruitment and Participants to Date

On May 21, 2019, of 58 individuals who were sent the invitation and survey link, 47 opened the invitation, 10 did not, and 1 opted out. Among these, 40 (69%) provided complete data, which represents 48% of our recruitment goal (40/84). The median time to complete the round 1 questionnaire was 1 h 55 min.

Respondents with complete data included 15 PLHIV and 25 providers, with 24 individuals from Canada and 16 from France. Among providers, there were 18 women and 7 men. Those in Canada were from Montreal (n=11), Toronto (n=4), and Vancouver (n=1). Those in France were from Paris (n=8) and Clermont Ferrand (n=1). The provider categories represented were pharmacist (n=8), nurse (n=7), physician (n=6), psychiatrist or psychologist (n=2), social worker (n=1), and CBO staff (n=1). Their year of birth ranged from 1955 to 1988. Over half had 15 or more years of experience treating PLHIV (13/25) and worked exclusively in a hospital setting (14/25). Among PLHIV, there were 7 women, 7 men, and 1 transgender person. They were from Montreal, Canada (n=9), and Clermont Ferrand (n=4) and Paris, France (n=2). Their year of birth ranged from 1947 to 1999. Approximately half had immigrated to their country of residence (7/15) and described their sexual orientation as heterosexual (8/15). Over a quarter (4/15) had ever injected drugs. All were currently on ART, with a quarter (3/14) reporting not being satisfied with their latest ART regimen.

Study Duration and Deliverables

From the scale up of recruitment (April 2019), the Delphi is expected to be led over 6 months. Study findings will be communicated through peer-reviewed publications, conference presentations, and other forms of knowledge dissemination (eg, academic rounds and Web-based reports in partnership with CBOs).

Discussion

To our knowledge, this is the first Delphi to seek consensus on the most important and clinically actionable barriers to ART adherence, drawing on a relatively large and diverse panel of HIV patients and providers. For the e-PROM's intended use in routine HIV care in Canada and France, the Delphi will serve to identify items that should be accorded priority or that require revision for clarity. Country and language group differences in ratings will also provide indications of the crosscultural validity of the measure items. Essentially, this Delphi will engage

important stakeholders in decision making about the measure's final content, helping to ensure its utility and adoption.

Routine e-PROM collection in HIV health service provision is in its infancy, despite notable initiatives [8,45,46]. The clinical use of PROMs could have cascading effects on the delivery and outcomes of care, including potentially improving patient-provider communication, self-management, and adherence [47]. Importantly, for HIV treatment, it could help it achieve its goals not only of viral suppression, but also of quality of life [4]. Evaluating these potentialities is a part of our e-PROM research program.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Untitled.

[PPTX File, 330KB - resprot_v8i8e12836_app1.pptx]

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Abbreviations

ART: antiretroviral therapy
CBO: community-based organization
CIHR: Canadian Institutes of Health Research
e-PROM: electronic PROM
I-CVI: item-content validity index
PLHIV: people living with HIV
PROM: patient-reported outcome measure
REB: research ethics board
SPOR: Strategy for Patient-Oriented Research

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Protocol

Predictors Linking Obesity and the Gut Microbiome (the PROMISE Study): Protocol and Recruitment Strategy for a Cross-Sectional Study on Pathways That Affect the Gut Microbiome and Its Impact on Obesity

Sophie Kindleysides[1], MSc; Rozanne Kruger[1], PhD; Jeroen Douwes[2], PhD; Gerald W Tannock[3,4,5], PhD; Nikki Renall[1,5], MSc; Joanne Slater[1], MSc; Blair Lawley[3,4], PhD; Anne-Thea McGill[6], PhD; Niamh Brennan[1], MSc; Moana Manukia[7], NZRN; Marilize Richter[1], PhD; Ridvan Tupai-Firestone[2], PhD; T Leigh Signal[8], PhD; Philippa Gander[8], PhD; Stephen R Stannard[1], PhD; Bernhard H Breier[1,4,5], PhD

[1]School of Exercise, Sport and Nutrition, College of Health, Massey University, Auckland, New Zealand

[2]Centre for Public Health Research, Massey University, Wellington, New Zealand

[3]Department of Microbiology and Immunology, University of Otago, Dunedin, New Zealand

[4]Microbiome Otago, University of Otago, Dunedin, New Zealand

[5]Riddet Centre of Research Excellence, Palmerston North, New Zealand

[6]School of Health & Human Sciences, Southern Cross University, East Lismore, Australia

[7]The Fono Health and Social Services, Auckland, New Zealand

[8]Sleep/Wake Research Centre, College of Health, Massey University, Wellington, New Zealand

Corresponding Author:
Bernhard H Breier, PhD
School of Exercise, Sport and Nutrition
College of Health
Massey University
Oteha Rohe Albany Highway
Auckland, 0745
New Zealand
Phone: 64 09 2136652
Email: b.breier@massey.ac.nz

Abstract

Background: The prevalence of obesity has increased substantially over recent decades and is associated with considerable health inequalities. Although the causes of obesity are complex, key drivers include overconsumption of highly palatable, energy-dense, and nutrient-poor foods, which have a profound impact on the composition and function of the gut microbiome. Alterations to the microbiome may play a critical role in obesity by affecting energy extraction from food and subsequent energy metabolism and fat storage.

Objective: We report the study protocol and recruitment strategy of the PRedictors linking Obesity and the gut MIcrobiomE (PROMISE) study, which characterizes the gut microbiome in 2 populations with different metabolic disease risk (Pacific and European women) and different body fat profiles (normal and obese). It investigates (1) the role of gut microbiome composition and functionality in obesity and (2) the interactions between dietary intake; eating behavior; sweet, fat, and bitter taste perception; and sleep and physical activity; and their impact on the gut microbiome, metabolic and endocrine regulation, and body fat profiles.

Methods: Healthy Pacific and New Zealand (NZ) European women aged between 18 and 45 years from the Auckland region were recruited for this cross-sectional study. Participants were recruited such that half in each group had either a normal weight (body mass index [BMI] 18.5-24.9 kg/m^2) or were obese (BMI ≥30.0 kg/m^2). In addition to anthropometric measurements and assessment of the body fat content using dual-energy x-ray absorptiometry, participants completed sweet, fat, and bitter taste perception tests; food records; and sleep diaries; and they wore accelerometers to assess physical activity and sleep. Fasting blood samples were analyzed for metabolic and endocrine biomarkers and DNA extracted from fecal samples was analyzed by shotgun sequencing. Participants completed questionnaires on dietary intake, eating behavior, sleep, and physical activity. Data were

analyzed using descriptive and multivariate regression methods to assess the associations between dietary intake, taste perception, sleep, physical activity, gut microbiome complexity and functionality, and host metabolic and body fat profiles.

Results: Of the initial 351 women enrolled, 142 Pacific women and 162 NZ European women completed the study protocol. A partnership with a Pacific primary health and social services provider facilitated the recruitment of Pacific women, involving direct contact methods and networking within the Pacific communities. NZ European women were primarily recruited through Web-based methods and special interest Facebook pages.

Conclusions: This cross-sectional study will provide a wealth of data enabling the identification of distinct roles for diet, taste perception, sleep, and physical activity in women with different body fat profiles in modifying the gut microbiome and its impact on obesity and metabolic health. It will advance our understanding of the etiology of obesity and guide future intervention studies involving specific dietary approaches and microbiota-based therapies.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618000432213; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370874

International Registered Report Identifier (IRRID): RR1-10.2196/14529

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KEYWORDS

diet; gut microbiome; body composition; women; overweight; obesity; physical activity; taste perception; sleep; metabolic diseases

Introduction

Background

Obesity is a global health issue of epidemic proportions [1]. The prevalence in New Zealand (NZ) has increased dramatically over the past three decades, with 1.2 million adults (32% of the population) currently being obese [2,3] and NZ ranking as the third most obese country in the Organization for Economic Co-operation and Development [4]. Obesity is related to significant health inequities, that is, Pacific peoples (69%) and Māori (50%) are disproportionately affected compared with the general population in NZ (32%), and rates are highest in the most deprived areas [5]. Recent trends in adult obesity in NZ show a significant rise in overweight (currently 64%) and obesity (currently 34%) in women, with major weight gains between the ages of 18 and 45 years [2,4]. This is of significant concern as increased adiposity in women of child-bearing age is associated with acute maternal, neonatal, and ongoing adverse health outcomes, including the perpetuation of increased obesity risk for the next generation [6]. Interventions to halt the epidemic have been unsuccessful [3,4].

Obesity is a complex, multifactorial condition contributing to a chronic prooxidant and proinflammatory state and to deterioration of glucose and lipid metabolism. It increases the risk of several noncommunicable diseases, including type 2 diabetes (T2D), cardiovascular disease (CVD), and some types of cancer [7,8]. Known contributing factors include imbalances in pathways of glucose and lipid metabolism that occur because of variations in quantity and quality of the diet, sedentary lifestyle, and genetic predisposition [9,10]. Obesity arises as a consequence of how the body regulates energy intake, energy expenditure, and energy storage, and it reflects a state of positive energy balance largely caused by westernized environmental pressures [11] resulting in an energy mismatch. This operates through dietary behaviors that do not trigger strong biological opposition [12]. A vicious cycle ensues, involving a state of excessive insulin secretion and a series of metabolic responses that produce systemic insulin resistance [13]. Desensitization to insulin action is accompanied by increased oxidative stress [14] and increased leptin secretion, inflammation, and a decreased ability to metabolize lipid and default energy storage as adipose tissue [15]. Furthermore, changes in the action of endocrine regulators including insulin, leptin, ghrelin, and glucagon-like peptide-1 (GLP-1) disturb appetite regulation in the obese state, rendering sustained weight loss difficult to achieve [16]. In this setting, the regulation of energy balance is biased toward protection against weight loss, further fat accumulation, and disease progression [12,17].

Current public health research to curb obesity is aimed at developing effective food and nutrition policies [11], promoting healthier food choices [18], and community-based interventions [19]. However, the notion that obesity is caused solely because we consume more energy than we expend does not fully explain the substantial increase in obesity [4,20]. Efforts to reduce obesity by inducing a negative energy balance, by counseling people to either eat less or exercise more, are often ineffective because of multiple physiological, behavioral, and social feedback loops [21]. Commonly cited causes of obesity include major changes in our food environment [3,11], which have led to overconsumption of inexpensive, highly palatable, energy-dense, and nutrient-poor foods. These changes in nutritional habits have been reported to influence the gut microbiome, which comprises the bacterial community of the bowel and its associated genetic endowment [4,22]. Current evidence suggests that the gut microbiome plays an important role in the regulation of energy homeostasis and the development of fat storage and obesity [23]. Proposed mechanisms include the microbiome's capacity to modify energy extraction from food and its ability to influence host signaling pathways that regulate energy metabolism [24]. Furthermore, the gut microbiome can influence satiety and food consumption through gut hormones that trigger endocrine feedback loops regulating appetite [24]. In turn, nondigestible dietary components affect the composition and metabolism of the gut microbiome [25].

The gut microbiome can be viewed as a critical modifiable link between diet and host and may offer new avenues for obesity

prevention [26]. Recent studies suggest that people with relatively less diverse microbiomes have higher overall body adiposity and more inflammation-associated characteristics, indicating a higher risk of metabolic diseases [27]. These findings suggest that microbiome complexity and diversity (or richness) may be predictive of the metabolic status of the host and may therefore function as a new biomarker of metabolic health. Dietary patterns that are associated with gut microbiome composition and dietary interventions can increase microbiome richness [25]. In addition, dietary habits may be the most critical factor influencing microbiome status, and therefore, it is critical to understand diet-microbiome interactions and their effect on human health. Finally, a number of other modifiable biological and behavioral factors in the complex causes of obesity appear to be linked with the gut microbiome: sweet and fat taste perceptions influence appetite and dietary behavior and are linked with body weight [28,29], and sleep duration and quality are linked with changes in appetite regulation and energy metabolism [30,31]. Disruption to the circadian biological clock leads to dysbiosis of the gut microbiome [32], and physical activity increases gut microbiome diversity [33].

Objectives

The PRedictors linking Obesity and the gut MIcrobiomE (PROMISE) study is the first to characterize the gut microbiome in 2 population groups with markedly different metabolic disease risk (Pacific and NZ European women) and different body fat profiles (normal and obese). The potential identification of distinct roles for taste perception, diet, sleep, and physical activity in modifying the gut microbiome and its impact on obesity will greatly advance our understanding of the etiology of obesity and contribute to the discovery of new therapeutic targets. The specific aims of the PROMISE study are to assess in 18- to 45-year-old Pacific and NZ European women: (1) the potential association of gut microbiome complexity and diversity, gene richness, and biochemical endowment in obesity and body fat distribution; (2) interactions between sweet, fat, and bitter taste perception, dietary intake and eating behavior, sleep or physical activity, and their impact on the gut microbiome, metabolic regulation, and body fat profiles; and (3) associations between biomarkers of biological and behavioral risk factors referred to above and specific body fat profiles. This study is designed to test the primary hypothesis that reduced gut microbiome diversity, but high energy-harvest capacity is a key biological driver of obesity and unhealthy body fat distribution in women, whereas greater gut microbiome complexity and gene richness is protective. The secondary hypothesis is that differences in diet, taste perception, sleep, and physical activity affect the associations between the gut microbiome, metabolic regulation, and body fat profiles. This paper reports the outline of the study protocol and the recruitment strategy. Details of the analytical procedures, study outcomes, and clinical measurements will be published elsewhere.

Methods

Conceptual Framework and Study Design

Comparisons between Pacific and NZ European women, who are known to vary the most in terms of physical, ethnic-cultural, and socioeconomic characteristics in NZ, will allow to assess whether findings are different between groups [2]. A further important distinction between the 2 ethnic groups is that a proportion of the participating Pacific women were born in the Pacific Island of origin, retaining their cultural lineage and dietary traditions, [34] and, as a consequence, may also have a distinctly different gut microbiome. This study involved the assessment of diet, taste perception, sleep, and physical activity, and we investigated the complex interactions between the gut microbiome and its impact on obesity, metabolic markers, and endocrine regulators, as described in Figure 1.

Figure 1 describes the central role of the gut microbiome in regulating energy homeostasis and body fat distribution. Aim 1 of this study investigates differential gut microbiome complexity, gene richness, and functionality between obese body fat profile women and normal body fat profile women stratified by ethnicity. For example, we investigate whether specific bacterial phyla are associated with obesity and/or characterized by relative abundances of genes associated with carbohydrate-active enzymes or whether a highly diverse microbiota with lower energy-harvest capacity is protective. Aim 2a investigates the fundamental influence of diet and food intake on body weight and body fat profile. We assess associations with gut microbiome complexity and functionality and explore whether specific microbiota profiles may be associated with specific dietary intakes or cultural dietary traditions. Aim 2b investigates interactions with sweet, bitter, and fat taste perception and Aim 2c explores the influence of sleep and physical activity. We assess independent effects or effect modification of taste perception, sleep, and physical activity and their impact on the gut microbiome and body fat profiles. Aim 3 examines interactions or effect modification with biomarkers and endocrine regulators and their relationships with food consumption, energy metabolism, and a range of risk factors that shape body fat profiles.

Participants

We have conducted a cross-sectional study in 174 Pacific women (who are known to have a high risk of obesity [5]) and 177 NZ European women (who are known to have a moderate risk of obesity [2,5]). Initial screening of body mass index (BMI), based on self-reported weight and height, was conducted on the Web, in person, or via the phone (Figure 2). The 351 participating women, aged 18 to 45 years, were selected such that half in each ethnic group had a normal body fat profile (BMI 18.5-24.9 kg/m^2) and the other half an obese body fat profile (BMI ≥30.0 kg/m^2), while recognizing that people with the same BMI can have substantial heterogeneity of body composition and metabolic disease risk factors [35,36].

Figure 1. The central role of the gut microbiome in regulating energy homeostasis and body fat distribution.

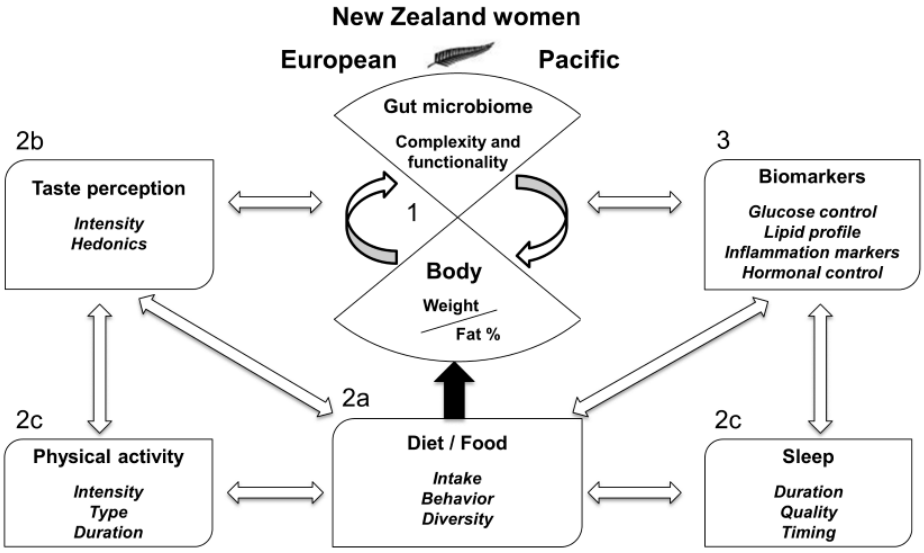
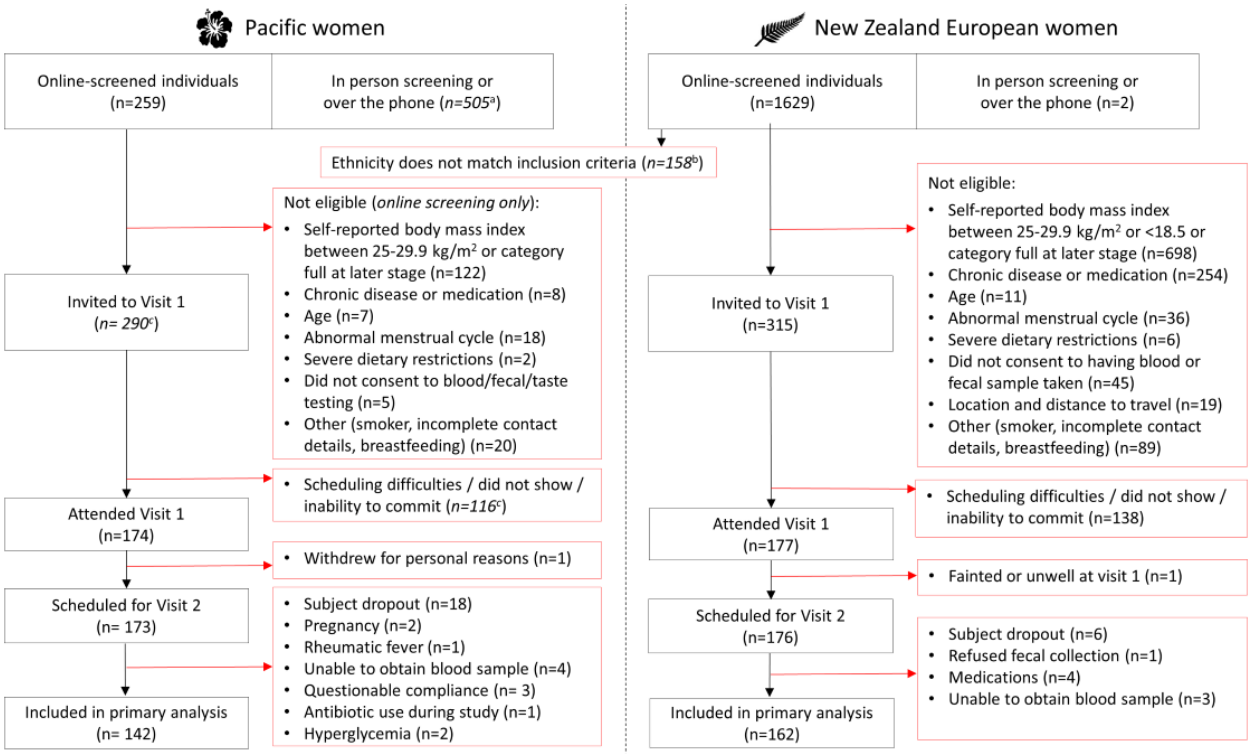


Figure 2. Flowchart describing the recruitment process of the PROMISE study. "a" indicates approximated value for Pacific women in-person screening or over the phone. "b" indicates that ethnicity inclusion was based on Pacific women requiring one parent of full Pacific ethnicity or New Zealand (NZ) European women having lived in NZ for a minimum of 5 years with European parents. "c" indicates approximated values since the majority of study bookings were managed over the phone.



Ethics

The study was approved by the Southern Health and Disability Ethics Committee (16/STH/32). This trial was registered at anzctr.org.au (ACTRN12618000432213). All participants were informed in detail about the procedures and measurements and gave written consent. Access to data is restricted to the immediate research team, and only coded data are used for analysis.

Inclusion and Exclusion Criteria

The inclusion criteria included age 18 to 45 years, being postmenarche and premenopausal (as defined by a regular menstrual cycle for the last year), ethnicity (self-identified Pacific ethnicity and having at least one parent of Pacific ethnicity or self-identified as NZ European ethnicity and having lived in NZ for a minimum of 5 years), written informed consent, willingness to comply with study requirements, and being generally healthy. The exclusion criteria included BMI

outside of the predefined normal or obese BMI ranges, pregnant or lactating, presence of any diagnosed chronic illness (eg, T2D and CVD), previous bariatric surgery, severe food allergies, medication that could interfere with appetite or the immune system (eg, appetite suppressants and corticosteroids), current smoker, severe dietary restrictions or avoidances (eg, vegan), and antibiotic use during the last month.

Participant Recruitment

The Auckland region has a culturally diverse population of 1,534,000, of which approximately 15% are Pacific peoples and 59% NZ European [37]. Health studies sometimes fail to address, or are not appropriately sensitive to, the cultural needs of the participants in terms of the recruitment approach or implementation of the study [38]. We therefore developed a partnership with The Fono, a large Pacific primary health care and social services organization based in Auckland, to integrate culturally appropriate recruitment and research procedures. This included the appointment of a senior Pacific nurse to lead the recruitment and support the data collection and management of the Pacific arm of the study. We also advertised on Pacific Facebook pages and contacted a wide range of special interest and cultural websites; however, we had little uptake from the Pacific organizations or groups that we contacted. As a result, Pacific women were mostly recruited in-person or by phone through the Pacific nurse (see Results). Other recruitment strategies included attending cultural festivals (ie, Pasifika festivals) and other cultural or preorganized events. Another successful strategy was recruiting Pacific students through the University Pacific networks. An additional *Me'a'ofa* (gift or donation) was offered to participants who could successfully enroll another participant who met the inclusion criteria and completed the study, thus enabling recruitment through existing networks. The services of 2 recruitment agencies, PRIME Research Ltd and Consumer Link, were also employed to support the recruitment of Pacific women with a BMI less than or equal to 24.9 kg/m^2. This was a successful strategy because previous networks were exhausted for this group of participants.

NZ European women typically heard of our study through Web-based advertisements such as Facebook community pages or *public figure* pages (well-known NZ nutritionists, etc), work or university email lists, or other social media sources (see Results). A number of Facebook pages, including local public figure pages, shared details of our study and endorsed the research on our behalf. Community Facebook pages (suburbs around Auckland, local businesses, etc) allowed for wide reach across the Auckland region. In contrast to Pacific women, social media (ie, Facebook) was a highly successful method for NZ European recruitment.

Participant gratuity (NZD $100 gift voucher including options for petrol, shopping center, and supermarket vouchers) was handed out at the end of visit 2 to encourage study completion and the return of all home-use devices and data.

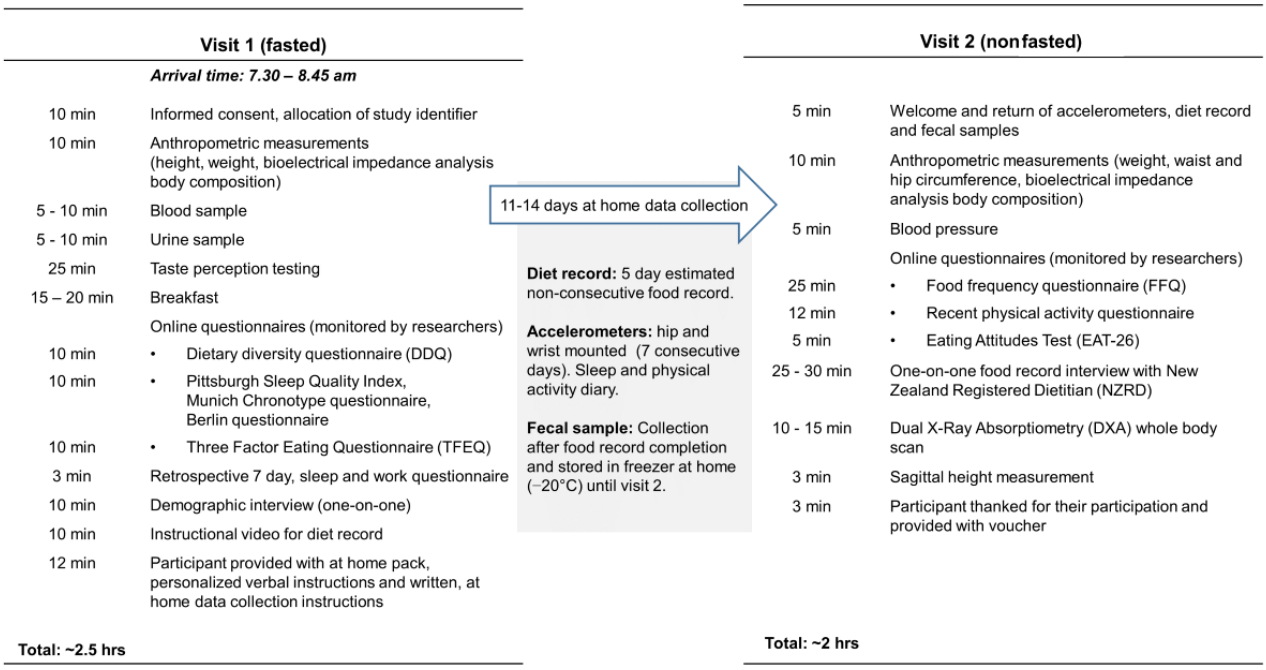
Study Procedures

The PROMISE study was conducted at the Massey University Human Nutrition Research Unit in Auckland, NZ, between July 2016 and September 2017. All eligible participants attended the research unit on 2 occasions, 11 to 14 days apart (Figure 3), where they completed a series of scheduled tasks. Between visits, participants completed the at-home data collection protocols described below. For Pacific women, we ensured that the Pacific nurse was present throughout the duration of Pacific participants' initial visits. She also performed the phlebotomy procedures for all Pacific participants and addressed all concerns about any aspects of the study that were raised. All Pacific participants were offered door-to-door transport to and from the research unit to enable participation in the study and to reduce the likelihood of *dropouts*.

At visit 1, participants were welcomed, asked to carefully read and sign a consent form, and had the opportunity to ask questions before commencing the study. Each participant was then allocated a unique study identifier (ID). Participants completed a one-on-one interview with a researcher to obtain a range of demographic and health information, including the number of biological children, household and personal income, occupation, work patterns, participants' birth weight and delivery method (if known), dietary supplement use, frequency of alcohol consumption, and recruitment method.

Figure 3 presents an overview of the PROMISE study visits and the sequence and timing of procedures. Visit 1 included the consent process, blood and urine sampling, taste perception testing, questionnaires, and instructions for at-home data collection. Participants collected data at home for approximately 11 to 14 days. At-home data collection included a 5-day nonconsecutive estimated food record, measurement of sleep and physical activity, and fecal sample collection. Visit 2 included delivery of all at-home collected data, body composition measurements by DXA, questionnaires, and the one-on-one food record interview.

Figure 3. Overview of the PRedictors linking Obesity and gut MIcrobiomE (PROMISE) study visits and schedule.



Blood Samples

Blood samples were obtained between 7:30 am and 9:00 am (after overnight fast, 10-15 hours), by an experienced phlebotomist. A tourniquet was applied moderately to the arm before venipuncture. Blood was drawn into 4 vacutainers (maximum total blood volume was 30 mL), to obtain serum and plasma for analysis of metabolic markers and endocrine regulators. Ethylenediaminetetraacetic acid (EDTA) 10 mL vacutainers (Becton Dickinson) were used for whole blood and stored immediately in a −80° C freezer before the remainder of the sample was placed on ice. The serum vacutainer was left to stand between 30 and 60 min at room temperature (18° C) to clot before centrifugation (10 mL, Becton Dickinson). For endocrine regulators, an additional plasma sample (2 mL Becton Dickinson vacutainer P800 EDTA, aprotinin, and dipeptidyl peptidase IV) was collected. The latter and all other vacutainers were placed on wet ice immediately after collection until centrifugation. Vacutainer tubes were centrifuged at 1500 g for 15 min at 4° C within 1 hour after blood samples were taken. Aliquots of plasma (23 aliquots, 120-500 µL) and serum (6 aliquots, 500-1300 µL) were transferred into prelabeled 1.5 mL microcentrifuge tubes (Eppendorf safe-lock polymerase chain reaction clean tubes) and cryovials (Cryo.S Greiner Bio-One, GmbH) and stored immediately at −80° C. Blood samples were analyzed for a range of biomarkers (eg, plasma glucose, insulin, glycated hemoglobin, lipids, and liver function tests), inflammation markers (eg, high-sensitivity C-reactive protein, interleukin 6 and tumour necrosis factor alpha), and endocrine regulators (eg, GLP-1, ghrelin, leptin, and adiponectin).

Urine Samples

After completion of blood collection, participants were required to collect a fasting, midstream urine sample. Research staff provided a urine container (BD Vacutainer Urine Collection Cup) labeled with their unique participant ID, cleansing wipes, and gloves. Once urine was collected, participants were asked to place their urine sample container on wet ice inside a clearly labeled polystyrene box before it was further processed by research staff. Midstream urine (14 mL) was pipetted into a prechilled 15 mL falcon tube. Urine samples were centrifuged at 1500 g for 15 min, at 4° C, to remove cellular particles and debris [39]. Ten aliquots of 1000 µL were transferred to each cryovial (Cryo.S, Greiner Bio-One, GmbH) and then transferred to −80° C storage for later metabolomics analysis.

Anthropometric Measurements

At visit 1, anthropometric measurements included stretched height and fasting weight measurements. All anthropometric measurements were conducted using the International Society for the Advancement of Kinanthropometry (ISAK) protocol [40]. All research staff conducting these measurements were level 1 ISAK trained. BMI was calculated using the Quetelet index (weight/height^2). At visit 2, waist and hip circumferences were measured with a Lufkin W600PM flexible steel tape with the participant in a relaxed standing position with their arms folded across their chest. Sagittal abdominal diameter was measured at the umbilicus level using the Holtain-Kahn Abdominal Caliper (Holtain Ltd) and assessed in a supine position. Bioelectrical impedance analysis (InBody230) was used to assess body composition at both visits 1 and 2. Body composition measurements were performed using dual-energy x-ray absorptiometry (DXA; Hologic QDR Discovery A, Hologic Inc with APEX V. 3.2 software) at visit 2 to accurately assess body composition profiles in terms of total and regional fat mass. Before DXA scanning, participants were asked to remove their jewelry and if they were pregnant or had a pacemaker or any metal implants. All staff who conducted DXA scanning procedures had Australian and NZ Bone Mineral Society clinical densitometry accreditation.

Blood Pressure

At visit 2, resting blood pressure was measured with an Omron digital blood pressure monitor (Omron HEM-907, Omron Healthcare Inc) using one of 2 arm cuff sizes (22-32 cm or 32-48 cm). In addition, a record was kept of each participant's pulse. Three measurements were taken consecutively at 1-min intervals. The mean of the second and third measurements was used to calculate systolic and diastolic blood pressure [41].

Dietary Intake and Behavior

Dietary intake was assessed for energy, macro- and micronutrient intakes, distribution of food intake throughout the day, and food choice. Our primary method for obtaining current dietary intake data was the gold-standard prospective, 5-day, food record [42-44]. The 5-day estimated food record included 2 weekend days and 3 weekdays. Estimated rather than weighed food records were used to improve adherence and to reduce participant burden [45,46]. Each participant received training for estimating and documenting portions, and every food record was reviewed by an NZ-registered dietitian before a one-on-one, in-depth discussion with the participant to clarify portions of foods consumed, cooking methods, brands of food products reported, and any other ambiguities. Visual portion book aids, household measures (eg, metric cups and spoons), and Web-based tools were used to confirm specific portion sizes and brands consumed, respectively. During these one-on-one interviews, standardized diet behavior-related questions were asked such as intentional meal skipping, snacking behaviors, and food preferences. These detailed sessions were critical to ensure accurate dietary data were captured [47].

It is often debated that all dietary assessment instruments are vulnerable to measurement errors, and significant improvements of dietary intake data quality can be achieved when different dietary intake recording methods are combined, especially combining food recording with food frequency questionnaires (FFQs) [42]. The validated semiquantitative New Zealand Women's Food Frequency Questionnaire (NZWFFQ) that was adapted from the FFQs used in the National Nutrition Survey NZ [43,44,48,49] was also completed by participants at visit 2. This covered dietary intake retrospectively across the last month, including the days that the 5-day food record was completed, to ensure that the range of actual and usual intakes were captured [42,50]. The 220-item NZWFFQ was administered using a Web-based questionnaire hosted on SurveyMonkey survey software, and live progress was monitored by research staff.

Nutrient analysis of the food record and FFQ data was performed using the Foodworks 9 (Xyris Software Pty Ltd) dietary analysis software, which uses FOODfiles 2016 (developed by the NZ Institute for Plant & Food Research and the NZ Ministry of Health) as a reference food composition table for analysis. In addition, the Xyris database AusFoods 2017 and AusBrands 2017, which are based on the Australian food composition databases AUSNUT 2011-13 (developed by Food Standards Australia New Zealand) were used. The data will be used to assess dietary adequacy in terms of energy and nutrient intakes using the current Australia/New Zealand nutrient reference values [51].

Participants completed the Dietary Diversity Questionnaire to assess food choices and dietary diversity, the Eating Attitudes Test (EAT-26) questionnaire to assess eating disorder risk, and the Three Factor Eating Questionnaire [52] to assess eating behavior in terms of cognitive dietary restraint (restraint), disinhibition of control (disinhibition), and susceptibility to hunger (hunger) by calculating scores for these dimensions and their subcategories.

Taste Perception

At visit 1, taste perception testing was conducted in a fasting state in individual testing booths at room temperature (20° C), before consuming breakfast. Participants were individually trained on the testing procedure and how to use general labeled magnitude scales [53,54] to rate the intensity and hedonic liking of sweet, bitter, and fat taste stimuli. Four distinct concentrations of glucose (30 g/L, 60 g/L, 120 g/L, and 240 g/L), quinine (0.008 g/L, 0.016 g/L, 0.03 g/L, and 0.06 g/L), and milk fat samples (3.3%, 11.8%, 20.3%, and 37.3% fat) were assessed using water as the control measure. Participants rated each solution by tasting the whole 10 mL of sample. They first rated the water stimuli (control, labeled *sweet*), followed by all sweet taste stimuli, before moving on to bitter taste stimuli and then milk fat stimuli. All stimuli were labeled with a 3-digit number, and the order was randomized within the tastant set. Participants had to rinse their mouth with water between samples. A ranking task was also administered for glucose, quinine, and milk fat samples to evaluate taste sensitivity [55], which was administered at the end of each tastant set. Ranking task stimuli were presented as a set of 4 distinct concentrations, labeled with unique 3-digit numbers to be ranked from the lowest to highest concentration (ie, 30 g/L, 60 g/L, 120 g/L, and 240 g/L).

Physical Activity and Sleep

To objectively measure sleep and physical activity, participants were fitted with 2 accelerometers during visit 1, 1 hip-mounted w-GT3X accelerometer (Actigraph), to measure physical activity, and a wrist-worn AW2 actiwatch (Phillips Respironics) to measure sleep. Participants were instructed to wear the accelerometers on their hip and nondominant wrist continuously (24-hour protocol) for the following 7 days, except while bathing or participating in water activities such as swimming. During this 7-day collection period, participants recorded in a provided diary the time they woke up each morning and went to sleep each night, as well as any intentional physical activity they engaged in [56]. At visit 2, participants also completed physical activity and sleep questionnaires, including the Recent Physical Activity Questionnaire [57], the Pittsburgh Sleep Quality Index [58], the Berlin questionnaire for sleep apnea [59], and their chronotype was assessed by the Munich Chronotype Questionnaire [60].

Fecal Samples

Fecal samples were collected by participants at home during the period between visits 1 and 2. At the end of visit 1, participants were briefed on how to collect fecal samples and were provided with a collection kit. This kit contained 2 prelabeled screw-top containers with a scoop in the lid (LBS3805 25 mL, ThermoFisher NZ), 2 larger prelabeled plastic

containers (LBS30130 130mL PP, ThermoFisher NZ), kidney dishes, gloves, zip-lock plastic bags, ice-sheets, chiller carry bag, and detailed written instructions. Participants were given an individualized schedule for food record and accelerometer data collection days, with the fecal sample needing to be collected after completion of the food record. Participants collected 2 separate, *walnut-sized* aliquots, from the same fecal sample and were asked to write down the time and date the aliquots were collected. The outer (larger) container was filled with 2 to 3 cm of cold water and the smaller container was placed inside the larger, to create a water jacket. Samples were then placed immediately in their household freezer (−20° C) and transported inside the chiller bag with ice packs when returning to the research unit at visit 2. Similar fecal sample collection methods have been utilized in a range of previous studies [61].

Gut Microbiome and Bioinformatics

DNA was extracted from fecal samples using methods described in the Human Microbiome Project [62]. In brief, microbial cells in fecal homogenates were physically disrupted by bead-beating, and then DNA was purified using a Mo Bio PowerSoil DNA isolation kit. The DNA was checked for quantity and quality using a combination of gel electrophoresis, nanodrop spectrometry, and Qubit fluorometry. The DNA was shotgun sequenced by NZ Genomics Ltd using Nextera library preparation and pools of 12 barcoded samples run per lane on an Illumina HiSeq 2500 instrument (Illumina).

Gut microbiome sequence data were analyzed using recognized computation (bioinformatics) tools [27]. These tools include the preparation of species-sampling curves that are the classic means of evaluating ecological richness (alpha diversity—biodiversity). As the genomes of all microbial species present in the microbiota were sequenced as small DNA fragments, both phylogenetic (describing what kinds of microbes are there and their relative abundances; MetaPhlAn2, QIIME v2) and functional (the biochemical capacity encoded in the metagenome; HUMAnN2) information are available [61].

Deprivation Index

Deprivation index was assessed in this study as a measurement of socioeconomic status. New Zealand Deprivation Index 2013 (NZDep2013) combines census data relating to home ownership, housing, qualifications, income, employment, access to transport, communications, and family structure [63]. NZDep2013 provides a deprivation score for each meshblock in NZ. Meshblocks are the smallest geographical area defined by Statistics NZ, with a population of around 60 to 110 people. NZDep2013 groups deprivation scores into deciles, where 1 represents the areas with the least deprived scores and 10 the areas with the most deprived scores. Therefore, a value of 10 indicates that a meshblock is in the most deprived 10% of areas in NZ.

Power Calculations

We have based our power calculation on previous studies involving metagenome-based measures of gene richness (gene counts) of fecal microbial communities [25,27] where individuals were categorized into clusters of high or low gene counts. Individuals in the low–gene count cluster may be at increased risk of progressing to obesity-associated comorbidities. On the basis of previous studies [27], we assumed the average gut microbiome complexity and gene richness in normal body fat profile women to equate to 640,000 genes. We then assumed a standard deviation of 350,000 in both normal and obese body fat profile women [25,27]. On the basis of these assumptions, we will have 76% power to detect a difference of 25% between both groups (68 per group). We will have 99% power to detect a difference of 40%, as previously observed in a European study [27]. We assumed that 33% of women have *abnormal* taste perception [28,29] or dietary intake [25], and 33% of women with *normal* taste perception and dietary intake have reduced gut microbiome complexity and functionality. On the basis of these assumptions, we will have 97% power to detect a 2-fold difference between both groups. We would have 83% power to detect the same difference if 25% of women with *normal* sweet and fat taste perception or dietary intake had reduced gut microbiome complexity. All power calculations are based on analyses for each ethnic group separately, as differences in associations between ethnic groups may exist.

Statistical Analyses

Descriptive statistical methods are used to summarize gut microbiome complexity and functionality; dietary intake and behavior; sweet, fat, and bitter taste perception; sleep, physical activity; and biomarkers. Differential gut microbiome complexity and gene richness are analyzed between obese body fat profile women and normal body fat profile women stratified by ethnicity using linear regression analyses. We also assess associations between gut microbiome complexity and functionality and biological and behavioral factors described above. Logistic regression analyses are used to compare reduced versus high gut microbiome complexity and gene richness, based on cut points employed in other studies. We will use multiple regression analysis to assess the independent effects of the biological and behavioral factors and perform stratified analyses to assess effect modification (or interactions). All analyses will be adjusted for potential confounders (socioeconomic position, age, etc).

Results

Recruitment of Pacific and New Zealand European Women

The order of recruitment completion of the main groups of study participants was as follows: (1) NZ European BMI 18.5 to 24.9 kg/m^2; (2) Pacific BMI greater than or equal to 30.0 kg/m^2; (3) NZ European BMI greater than or equal to 30.0 kg/m^2; and (4) Pacific BMI 18.5 to 24.9 kg/m^2. Although the criteria for recruitment of Pacific women generally required that both parents were of Pacific descent, 10% of the Pacific participants recruited for the PROMISE study were accepted if they had only one parent of Pacific descent but identified clearly as being primarily of Pacific ethnicity. The NZ European BMI greater than or equal to 30.0 kg/m^2 group and the Pacific BMI 18.5 to 24.9 kg/m^2 group required additional advertising and specifically targeted recruitment strategies in comparison with the other 2

groups of women. The specific recruitment methods and the number of participants recruited through each approach are summarized in Table 1.

Researchers made a number of observations during the study visits that characterized some of the logistical challenges during the recruitment period of the study. For Pacific women, key motivations to participate in the study included, but were not limited to, personal contact with the study facilitators through the Pacific community, *Me'a'ofa* (gift or donation), and interest in the outcomes of the study. For NZ European women, key motivations to participate in the study included, but were not limited to, interest in individual measurements such as blood markers (eg, cholesterol) and body composition measurements (eg, DXA scan), interest in the gut microbiome, *Me'a'ofa* (gift or donation), and interest in the nutrition-related measurements in the study.

General Characteristics of the Predictors Linking Obesity and the Gut Microbiome Study

A total of 351 participants were eligible to participate in the study (Figure 2). An overview of basic phenotype characteristics of the PROMISE study participants is presented in Table 2. Although our main target was to recruit participants with a normal BMI (18.5-24.9 kg/m^2) and an obese BMI (≥30.0 kg/m^2), we also recruited an additional 54 participants in the overweight BMI (25.0-29.9 kg/m^2) range. The overweight BMI groups were included in this study because, first, some participants had incorrectly assessed their own height and weight before they arrived at the human nutrition research unit, and second, to offset the enormous difficulties of recruiting normal BMI Pacific women.

Table 1. Recruitment methods, examples, and the number of participants recruited (feedback from enrolled participants only, N=351).

Recruitment method	Examples	Number recruited[a]	
		Pacific	New Zealand European
The Fono Primary Healthcare Service (West Auckland)	Pacific staff members recruited through their database and wider community. Transport to and from research clinic provided. Radio interview (Radio Samoa 1593 FM; Tongan segment discussing the *gut microbiome*)	102	N/A[b]
Participant word of mouth	University students, previous PROMISE[c] participants (interest increased with *Me'a'ofa* [gift or donation])	36	21
Community/University Facebook pages/Special interest pages	Auckland (New Zealand) city central and surrounding suburbs, (approximately 38 Facebook pages; with repeat posts) and Pacific Heartbeat	4	52
Public figures Facebook pages[d]	Local nutritionists, sports celebrities	2	26
University/work email lists	Massey University (New Zealand), The University of Auckland (New Zealand), New Zealand Police	3	15
Hospital staff newsletter/magazine	Auckland hospital network and email lists	2	15
Job advertisement site or volunteer page	Job search website, volunteer to participate in research website, student job search website	5	5
One-on-one recruitment (handing out flyers)	University orientation week, early childhood centers, schools	1	9
Websites	University website article, The Fono Primary Healthcare Service	1	3
Magazine articles[e]	National magazines (ie, nutrition, current affairs, and lifestyle). Articles mentioned current study and provided contact details	0	9
Festivals	Local Pacific festivals (ie, Polyfest 2017, Pasifika 2017)	4	1
Posters[e]	Universities, hospitals, health clinics, libraries, cafes, leisure centers, public swimming pools, gyms, community boards, supermarket notice boards	0	11
Recruitment companies	Consumer paid market research databases to recruit Pacific women with a body mass index of 18.5-24.9 kg/m^2 only	13	N/A
Instagram	Instagram *story* on local nutritionists/public figure Instagram feeds	1	2
Local newspaper articles/website[e]	Local free newspapers	0	3
Internal database of contacts[e]	List of names recontacted who previously completed a similar trial [43] (note: filtered to contact difficult body mass index categories only)	0	3
Neighbourly, Twitter[e]	Local suburb page Web noticeboard, PROMISE study twitter account (@promise_study)	0	2

[a]Level of recruitment based on attendance at visit 1 of the PROMISE study.

[b]N/A: not applicable.

[c]PROMISE: PRedictors linking Obesity and the gut MIcrobiomE.

[d]Public figure pages used at the stage of recruitment where NZ European BMI ≤24.9 kg/m^2 category was full; eg, one local nutritionist Facebook post resulted in 221 completed screening questionnaires, which resulted in 17 NZ European BMI ≥30.0 kg/m^2 participants.

[e]Advertisement method successful across NZ European women only.

Table 2. General phenotype characteristics and New Zealand Deprivation Index 2013 of the PRedictors linking Obesity and the gut MIcrobiomE (PROMISE) study participants who completed the study protocol (N=304).

Variable	Pacific women (n=142)	New Zealand European women (n=162)
Normal (BMI[a] 18.5-24.9 kg/m^2)		
Participants, n	36	79
Age (years), mean (SD)	24 (6)	30 (6)[b,c]
BMI (kg/m^2), mean (SD)	23.0 (1.6)	22.0 (1.5)[b]
Waist circumference (cm), mean (SD)	74.3 (4.3)	72.5 (4.9)
Hip circumference (cm), mean (SD)	100.6 (5.6)	97.0 (5.9)[b]
WHR[d], mean (SD)	0.74 (0.03)	0.75 (0.05)
Systolic BP[e] (mmHg), mean (SD)	109.4 (9.88)	111.7 (10.31)
Diastolic BP (mmHg), mean (SD)	68.5 (5.86)	70.6 (8.86)
NZDep2013[f], mean (SD)	7 (3)	4 (3)[b]
Overweight (BMI range 25.0-29.9 kg/m^2)		
Participants, n	33	13
Age (years), mean (SD)	26 (7)	28 (8)
BMI (kg/m^2), mean (SD)	27.5 (1.6)	26.4 (1.8)
Waist circumference (cm), mean (SD)	83.1 (5.1)	79.6 (5.9)
Hip circumference (cm), mean (SD)	108.6 (4.8)	106.9 (5.8)
WHR, mean (SD)	0.77 (0.05)	0.75 (0.04)
Systolic BP (mmHg), mean (SD)	113.1 (7.27)	115.0 (6.88)
Diastolic BP (mmHg), mean (SD)	70.6 (7.83)	69.5 (3.90)
NZDep2013, mean (SD)	7 (3)	4 (2)[b]
Obese (BMI range ≥30.0 kg/m^2)		
Participants, n	73	70
Age (years), mean (SD)	25 (6)	34 (7)[b]
BMI (kg/m^2), mean (SD)	36.9 (5.4)	34.3 (3.0)[b]
Waist circumference (cm), mean (SD)	100.8 (11.4)	99.3 (8.9)
Hip circumference (cm), mean (SD)	123.7 (10.9)	121.6 (7.5)
WHR, mean (SD)	0.81 (0.06)	0.82 (0.06)
Systolic BP (mmHg), mean (SD)	119.6 (11.5)	121.9 (14.2)
Diastolic BP (mmHg), mean (SD)	78.9 (9.99)	81.1 (9.39)
NZDep2013, mean (SD)	8 (2)	5 (2)[b]

[a]BMI: body mass index.

[b]$P<.01$ was deemed statistically significant.

[c]Independent samples *t* tests were performed to determine differences between ethnicities.

[d]WHR: waist-to-hip ratio.

[e]BP: blood pressure.

[f]NZDep2013: NZ Deprivation Index 2013.

Discussion

Principal Findings

This paper reports the study protocol and the recruitment strategy of the PROMISE study, the details of the analytical procedures, study outcomes, and clinical and physiological measurements will be published elsewhere. The main objective of the PROMISE study is to characterize the gut microbiome in 2 population groups with markedly different metabolic disease risk (Pacific and European women) and different body fat profiles (normal and obese). The study describes the roles of taste perception, diet, sleep, and physical activity in women with different body fat profiles in modifying the gut microbiome and its impact on obesity and metabolic health. Only healthy participants were included in the study in accordance with strict inclusion and exclusion criteria. We established well-defined protocols of scheduled experimental conditions with standard operating procedures (SOPs) for all domains of the study. All participants followed the same SOPs according to specified timelines, and all specimen samples were treated identically. The main rationale for this approach was to collect high-quality data and to minimize variation related to data acquisition, data analysis, and sampling of biological specimens.

There is a dearth of data in populations at greatest risk of developing obesity. The PROMISE study will help to fill these gaps. Although a cross-sectional design will not infer causality [64], it is a highly efficient approach that will be able to identify distinct roles for diet, taste perception, sleep, and physical activity in modifying the gut microbiome and its impact on obesity and metabolic health. An additional strength of the PROMISE study is the recruitment of women from Pacific and European population groups. It allows us to assess potential differences and commonalities between population groups with markedly different metabolic disease risk profiles and will provide new insights and has the potential to contribute to novel hypotheses. A number of previous studies have presented convincing evidence that the gut microbiome may be a central modifiable link between diet and host and may be likely to offer new avenues to tackle obesity [22,25,26]. However, many important questions remain. First, how important is the ratio of the bacterial phyla *Firmicutes* to *Bacteroidetes*? Highly publicized studies reported low abundances of *Bacteroidetes* and higher abundances of *Firmicutes* as a characteristic of obesity [65]. However, later studies failed to find this association and, in general, meta-analyses show that most obesity-microbiome studies in humans to date have been underpowered to determine valid differences between groups [66]. In addition, there is increasing evidence that whole genome shotgun sequencing, as used in the PROMISE study, has multiple advantages compared with the 16S amplicon method used in many previous studies. The advantages of shotgun metagenomics sequencing include enhanced detection of bacterial species, increased detection of diversity, and increased prediction of the most dominant gene pathways that are present in the particular genes [67]. Furthermore, much of the previous work has been conducted in mice, and the few human studies available were small and need to be replicated in larger studies. Second, how strong is the association between low gene count clusters and obesity? Metagenomic measures of gene richness (gene counts) of gut microbial communities have categorized individuals into clusters of high or low gene count, but the exact nature of this relationship is not known [25,27]. Third, is there an association between relative abundances of bacterial species with obese or lean phenotypes in humans [68]? Fourth, is there an association between abundance of specific gut microbiota with dietary intake of particular food groups or dietary patterns [69,70]? Finally, do ethnic and/or cultural differences, sleep, and physical activity modify associations between the gut microbiome and obesity?

Given the cultural diversity of the participants, it was vital that research staff from the Pacific community were actively involved in performing the study to ensure the study was conducted in a culturally appropriate manner and to support the collection of quality data and successful outcomes [71]. Furthermore, there is convincing evidence that community-based participatory research approaches, involving community members and organizational representatives can overcome recruitment challenges and enhance the quality of a study [71-73]. The participation of a senior Pacific research nurse in the research team and the partnership with The Fono were invaluable in providing support and understanding from a participant perspective. In NZ, the essence of showing respect and kindness is described as *manaakitanga*, which encompasses hosting visitors with care, developing a nurturing relationship, and being a responsible host [74]. Adoption of *manaakitanga* within the framework of the PROMISE study, incorporating socially and emotionally grounded beliefs, enhanced participant engagement in what could commonly be perceived as a formal clinical research setting. Therefore, we recommend that future studies incorporate a range of strategies and culturally appropriate approaches to support community-based engagement throughout all aspects of the research [38].

Strengths and Limitations

A remarkable experience of the recruitment process was the success of using social media as a recruitment tool for NZ European women. Overall, we found that employing multiple recruitment methods, including social media (eg, community Facebook pages), newspaper advertisements, and business circulars (eg, work place email lists) gave this study a wider representation of the general population. It is important to keep in mind that although Auckland city has the highest population of resident Pacific peoples, the total number of Pacific women living in Auckland is much lower than that of NZ European women. In addition, many Pacific communities live in regions that are over 25 km away from the research unit such that transport issues were a significant barrier for some Pacific participants. Therefore, it was not surprising that Pacific women were more challenging to recruit than NZ European women. It has been recognized that barriers to participating in clinical research include fear and lack of trust in the study procedures or in research staff. In contrast, motivating factors include free health care access, feeling connected to the research outcomes that may support family or friends in the future (eg, developing treatments for specific diseases), and monetary incentives [72]. The PROMISE study team embraced these critical factors, paid attention to using appropriate language, and generated a

culturally and gender-appropriate setting during all procedures (ie, DXA scanning) to contribute to a positive experience for participants [72].

The recruitment of participants faced a number of challenges. For example, women with a high BMI may have felt less motivated to take part in obesity-related research because of a concern of negative evaluation, as reported previously [75]. Furthermore, difficulties in recruiting Pacific women with a normal BMI in this study were because of their low number within the general Pacific population, only 8% of adult Pacific women have a BMI between 18.5 and 24.9 kg/m^2 [5,37]. To address these barriers, additional efforts were made to advertise and recruit Pacific women into the PROMISE study. Therefore, we extended the recruitment range, especially for Pacific women, to include the overweight BMI range (25.0-29.9 kg/m^2). Furthermore, we increased the *Me'a'ofa* and provided transport to and from the research unit to encourage participation and completion of the study protocol. The disadvantage of such tailored recruitment approaches is the risk of increasing selection bias. Although we are not able to quantify the potential selection bias because of the differences in the success rate of the range of recruitment methods presented in Table 1, we have made every effort to ensure participants are representative of each population group [76]. Furthermore, we tailored our advertising and recruitment strategy in a way that was most culturally appropriate for each population group; it ensured participant engagement and motivation, which is known to enhance data quality and study completion [38,77].

Challenges of a cross-sectional study design include the temporality of single assessments and the potential bidirectional nature of some associations. Furthermore, multiple comparisons and a large number of assessments and outcome variables and the potential for complex interactions may require further stratification. However, the study design and recruitment emphasis on obese *versus* normal BMI categories in the PROMISE study is an efficient approach to identify and contrast biological parameters that are associated with obesity-related metabolic disease risk. Most previous studies have focused on only 1 or 2 aspects that may influence the gut microbiome and obesity. The comprehensiveness of the PROMISE study design and our multidisciplinary approach are a particular strength. It will greatly advance our understanding of the etiology of obesity and will guide future longitudinal studies and interventions involving specific microbiota-based therapies, linking the outcomes of our study with strategies for the design of foods that offer metabolic health benefits through changes of the gut microbiome.

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Authors' Contributions

BB, RK, JD, and GT developed the study concept and design and wrote the grant application for funding support. RF, PG, TLS, SS, BL, and ATMG contributed to the study design. NB, MM, SK, JS, NR, BB, RK, and MR played key roles in participant recruitment, the organization of the study, and data acquisition. BB and SK drafted the manuscript, and all authors contributed to and accepted the final version.

Conflicts of Interest

None declared.

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Abbreviations

BMI: body mass index
BP: blood pressure
CVD: cardiovascular disease
DXA: dual-energy x-ray absorptiometry
EDTA: ethylenediaminetetraacetic acid
FFQ: food frequency questionnaire
GLP-1: glucagon-like peptide-1
ISAK: International Society for the Advancement of Kinanthropometry
NZ: New Zealand
NZDep2013: New Zealand Deprivation Index 2013
NZWFFQ: New Zealand Women's Food Frequency Questionnaire
PROMISE: PRedictors linking Obesity and gut MIcrobiomE
SOP: standard operating procedure
T2D: type 2 diabetes
WHR: waist-to-hip ratio

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Protocol

Pathology Laboratory Surveillance in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmitted Infections and Blood-Borne Viruses: Protocol for a Cohort Study

Caroline van Gemert[1,2,3], MAppEpid, MPH, PhD[‡]; Rebecca Guy[4], PhD; Mark Stoove[1,2], PhD; Wayne Dimech[5], FRCPA; Carol El-Hayek[1], MSc; Jason Asselin[1], BSc, Grad Dip; Clarissa Moreira[1], MSc; Long Nguyen[1], BCom, GradCertSc; Denton Callander[4], PhD; Douglas Boyle[6], PhD; Basil Donovan[4], MD; Margaret Hellard[1,2,3,7,8], MD, PhD

[1]Burnet Institute, Melbourne, Australia

[2]Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia

[3]Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Australia

[4]The Kirby Institute, University of New South Wales, Sydney, Australia

[5]NRL, Melbourne, Australia

[6]Department of General Practice, The University of Melbourne, Parkville, Australia

[7]Doherty Institute, Melbourne, Australia

[8]Department of Infectious Diseases, The Alfred Hospital, Melbourne, Australia

[‡]on behalf of the ACCESS Collaboration

Corresponding Author:
Caroline van Gemert, MAppEpid, MPH, PhD
Burnet Institute
85 Commercial Road
Melbourne, 3004
Australia
Phone: 61 392822243
Email: caroline.vangemert@burnet.edu.au

Abstract

Background: Passive surveillance is the principal method of sexually transmitted infection (STI) and blood-borne virus (BBV) surveillance in Australia whereby positive cases of select STIs and BBVs are notified to the state and territory health departments. A major limitation of passive surveillance is that it only collects information on positive cases and notifications are heavily dependent on testing patterns. Denominator testing data are important in the interpretation of notifications.

Objective: The aim of this study is to establish a national pathology laboratory surveillance system, part of a larger national sentinel surveillance system called ACCESS (the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance). ACCESS is designed to utilize denominator testing data to understand trends in case reporting and monitor the uptake and outcomes of testing for STIs and BBVs.

Methods: ACCESS involves a range of clinical sites and pathology laboratories, each with a separate method of recruitment, data extraction, and data processing. This paper includes pathology laboratory sites only. First established in 2007 for chlamydia only, ACCESS expanded in 2012 to capture all diagnostic and clinical monitoring tests for STIs and BBVs, initially from pathology laboratories in New South Wales and Victoria, Australia, to at least one public and one private pathology laboratory in all Australian states and territories in 2016. The pathology laboratory sentinel surveillance system incorporates a longitudinal cohort design whereby all diagnostic and clinical monitoring tests for STIs and BBVs are collated from participating pathology laboratories in a line-listed format. An anonymous, unique identifier will be created to link patient data within and between participating pathology laboratory databases and to clinical services databases. Using electronically extracted, line-listed data, several indicators for each STI and BBV can be calculated, including the number of tests, unique number of individuals tested and retested, test yield, positivity, and incidence.

Results: To date, over 20 million STI and BBV laboratory test records have been extracted for analysis for surveillance monitoring nationally. Recruitment of laboratories is ongoing to ensure appropriate coverage for each state and territory; reporting of indicators will occur in 2019 with publication to follow.

Conclusions: The ACCESS pathology laboratory sentinel surveillance network is a unique surveillance system that collects data on diagnostic testing, management, and care for and of STIs and BBVs. It complements the ACCESS clinical network and enhances Australia's capacity to respond to STIs and BBVs.

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KEYWORDS

hepatitis; HIV; sexually transmitted diseases; laboratories; epidemiology; Australia

Introduction

Background

The burden of sexually transmitted infections (STIs) and blood-borne viruses (BBVs) compromises quality of life, sexual and reproductive health, and child health, and they can impose a significant financial burden on both the health system and household [1]. STIs—including chlamydia, gonorrhea, and syphilis—and BBVs—including hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV—remain a major public health problem in Australia. Australian notification data revealed that chlamydia and gonorrhea were the second and fourth most notified of all notifiable conditions in Australia in 2016, respectively, and the number of notifications for each has increased steadily since 2000. Infectious syphilis has also increased, with the number of notifications doubling between 2003 and 2017. The number of notifications from HIV has decreased in the last 5 years; however, ongoing study is needed to monitor infections in people who acquire HIV from heterosexual sex and in Aboriginal and Torres Strait Islander people. Chronic HBV infection has remained relatively stable; however, underdiagnosis remains a concern. An increase in HCV notifications was observed in 2015 and 2016, likely in relation to an increase in testing because of the availability of new direct-acting antiviral medications [2,3].

In 2016, the World Health Organization launched a series of global health sector strategies (2016-2021) that outlined goals for ending STIs [1], HIV [4], and viral hepatitis [5] by 2030. Surveillance is recognized as an essential component to measure progress made in each strategy. In many high-income countries, STI and BBV surveillance has traditionally encompassed passive surveillance (ie, case reporting). Passive surveillance is the principal method of STI and BBV surveillance in Australia whereby all states and territories have legislated the notification of all positive cases of select STIs and BBVs from clinicians and pathology laboratories to state and territory health departments [6]. The benefits and limitations of passive surveillance have been well documented; passive surveillance is relatively inexpensive, can cover large geographical areas, and is able to detect disease outbreaks; however, it only collects information on positive cases and notifications are heavily dependent on testing patterns [7,8]. Testing patterns are, in turn, dependent on recommendations and guidance, for example, in Australia, higher risk gay and bisexual men who have sex with men are recommended to be offered STI and BBV testing up to four times per year [9] and pregnant women are recommended to be screened for HBV and HIV, at a minimum [3,9]. Denominator testing data (ie, the total volume of tests conducted) are important in the interpretation of notifications but passive surveillance traditionally does not collect these data. In addition, STI and BBV infections are frequently asymptomatic and, therefore, diagnosis rates will underrepresent true incidence and prevalence.

Several high-income countries, including the United States and the United Kingdom, have implemented pathology laboratory surveillance systems to monitor STIs and BBVs [10-15]. Pathology laboratory surveillance, a form of sentinel surveillance, is used to complement passive surveillance whereby data are collected from a limited number of reporting (*sentinel*) sites. Sentinel surveillance systems are not intended to capture all testing or diagnostic data; rather, they aim to provide a representative sample of those at risk of infection [16]. Sentinel surveillance can be used to measure the burden of disease for infections that are not notifiable and to monitor priority populations in greater detail. Furthermore, when line-listed data are collected for individuals in a comprehensive sentinel surveillance system, a range of additional and more complex analyses are enabled. These include monitoring adherence to STI or BBV prevention and management guidelines (such as frequency of testing and retesting), outcomes of treatment and vaccination (such as HCV cure, HIV viral suppression, and HBV immunity), and other epidemiological outcomes such as incidence, which can be calculated using repeat testing methods.

Objective

Recognizing the importance of testing denominator data for surveillance, this study aims to establish a national pathology laboratory surveillance system, part of a larger national sentinel surveillance system called ACCESS (the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance). ACCESS was originally implemented in 2007 as a chlamydia-only system [17] and it demonstrated utility to monitor chlamydia testing and positivity in priority populations and sentinel health services and laboratories across Australia [17-22]. This paper describes the purpose, design, and potential of pathology laboratory surveillance in ACCESS.

Methods

Study Design and Aims

ACCESS involves a range of clinical sites (including sexual health clinics, general practice clinics, drug and alcohol services, community-led testing services, and hospital outpatient clinics) and pathology laboratories, each with a separate method of recruitment, data extraction, and data processing; this paper includes pathology laboratory sites only, and the establishment of clinical sites has been previously described [23]. ACCESS expanded in 2012 to capture all diagnostic and clinical monitoring tests for STIs and BBVs, initially from pathology laboratories in the 2 largest states in Australia (New South Wales and Victoria), and in 2016 expanded to capture data from at least one public and one private pathology laboratory in all Australian states and territories. The pathology laboratory sentinel surveillance system incorporates a longitudinal cohort design whereby all diagnostic and clinical monitoring tests for STIs and BBVs are collated from participating pathology laboratories in a line-listed format.

The aim of ACCESS is to underpin Australia's strategic response to STIs and BBVs by maintaining a surveillance system to monitor the testing, diagnosis, and management of these infections and evaluate the impact of relevant health interventions.

Setting

Australia has a system of both public and private pathology laboratory services with the organization of public pathology laboratories varying across jurisdictions. For example, in New South Wales, services are organized around hospital networks, whereas in Victoria, pathology laboratories operate through individual public hospitals. Public pathology laboratories also provide pathology services to some community-based services, including state and territory-funded sexual health services. Free access to public pathology services is jointly funded by the Australian state and territory governments principally through the National Healthcare Agreement. Private pathology services are the main provider of community-based pathology services. Private pathology laboratories operate specimen collection services across urban, rural, and remote parts of Australia and provide pathology services in several private hospitals on a contracted basis. Private pathology services in the community and in private hospitals are subsidized by the Australian Government through the Medicare Benefits Schedule [24].

Eligibility and Recruitment

As noted above, ACCESS was initially restricted to New South Wales and Victoria—Australia's most populous states—representing 32% and 26%, respectively, of Australia's total population of 23,401,892 in 2016 [25], but with the expansion in 2016, all public and private pathology laboratories are currently eligible to participate in ACCESS if they conduct STI and BBV testing, with ongoing recruitment of pathology laboratories at this time.

Information on the size and scope of pathology laboratories is maintained by NRL (formerly known as the National Serology Reference Pathology laboratory, a not-for-profit scientific organization that exists to improve the quality of pathology laboratories testing for infectious diseases). Sites will be selected based on their size, geographical coverage, and clinics that they serviced and will be contacted directly by ACCESS staff and invited to participate. In the initial expansion between 2012 and 2016, a total of 15 pathology laboratories were recruited, including 7 from New South Wales (4 public and 3 private) and 8 from Victoria (6 public and 2 private) representing 41% of the 37 pathology laboratories in those 2 jurisdictions that conduct and report HIV testing data via a quality assurance system [26], and include 971 collection centers (Figure 1). Following the expansion of ACCESS in 2016, 4 more pathology laboratories have been recruited from 3 jurisdictions, including the Australian Capital Territory, Queensland, and Tasmania, resulting in a total of 15 pathology laboratory services. Recruitment is ongoing in the remaining Australian states and territories. Pathology laboratories will receive an establishment payment of Aus $2000 and an annual payment of Aus $500 in subsequent years. This payment is intended to reimburse time and equipment required to establish and maintain data extraction.

Coordination and Governance

ACCESS is a collaboration among the Burnet Institute, Kirby Institute, and NRL. Table 1 provides the description of data extracted.

Data Extraction and Linkage

Filters will be used to extract tests related to the diagnosis or management of STIs (chlamydia, gonorrhea, and syphilis) and BBVs (HIV, HBV, and HCV). The extraction and interpretation of tests will be guided by several policies and guidelines, including the Australian STI Management Guidelines for Use in Primary Care [9], the National HIV Testing Policy [27], the National HCV Testing Policy [28], and the National HBV Testing Policy [29]. A list of variables required will be provided to each pathology laboratory to allow pathology laboratory database engineers to map the required variables from their individual pathology laboratory database (see Table 1). Laboratories throughout Australia use assays from different manufacturers and generally have internal selection processes for the selection of markers specific to their laboratory. Some networks of laboratories, especially in the private sector, have uniform selection of assay manufacturer or marker selection, but uniform selection is not universal and cannot be assumed.

Test data comprising 100 lines of data will be extracted initially and provided to the ACCESS team to ensure data items are mapped correctly. Deidentified, encrypted pathology laboratory testing data will then be extracted using GRHANITE data extraction software, developed by the Health and Biomedical Informatics Centre's GRHANITE Health Informatics Unit at the University of Melbourne [30]. Following installation of GRHANITE at each pathology laboratory, retrospective data from January 1, 2009, to the date of installation will be extracted. Subsequent data extraction will be scheduled monthly, with the previous month's data collected at each extraction. The accuracy of GRHANITE as a mechanism for data extraction is high; a 2012 review of extracted chlamydia test data from primary health clinics by GRHANITE reported that all chlamydia tests were identified and extracted [31].

Figure 1. Location of pathology laboratory collection centres in Victoria and New South Wales by Local Government Area, 2016. Note: Postcodes have been converted to Australian Local Government Areas for mapping purposes. Local Government Areas are shaded according to the size of the estimated resident population; darker colours have larger population sizes. Marker for laboratory location is proportional to the number of laboratories located in each local government area.

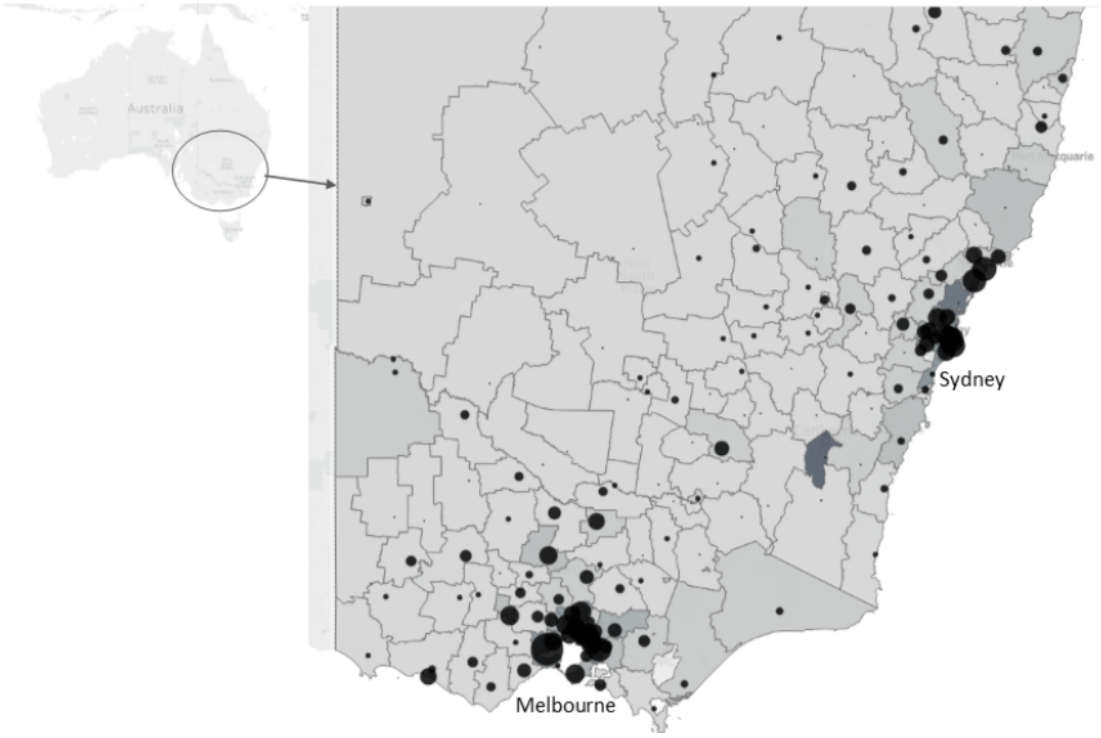

Table 1. Description of data extracted.

Domain	Data collected
Pathology laboratory	Pathology laboratory name and location
Patient	Generated unique patient identification number; Sex (Male/Female); Patient postcode; Year of birth; Patient ID number at requesting clinic
Request	Date of consultation; Requesting clinician provider number; Clinic name; Clinic postcode
Testing	Date of test; Specimen identification number at pathology laboratory; Pathology laboratory of origin; Test code; Specimen type; Specimen site; Test result; Notes

For each test, information will be extracted on patient demographics (patient sex, patient age at test, and patient postcode), request details (requesting clinician, clinician provider number, and date of test request), and testing details (including test name, specimen site, result, and date of test; Table 1).

GRHANITE will create a unique, encrypted, and nonreversible patient identifier for individuals within each pathology laboratory, using the available patient demographic data. To link the same individual, both within and between pathology laboratories, GRHANITE software will also generate statistical linkage keys (encrypted and nonreversible hash values) using a range of combinations including surname, first/given name, sex, date of birth, Medicare number, and postcode. The statistical linkage key will be created before data extraction and no identifiable data will be extracted. Using the GRHANITE linkage tool software, matches between statistical linkage keys will be identified. On the basis of these matches, a new linkage identification number will be assigned to each unique patient identifier to allow the identification of tests from the same individual within and between pathology laboratories.

Data Transfer and Storage

Encrypted data files will be received on the Burnet Institute databank server and imported into a Microsoft Structured Query Language Server database. Both the encrypted files and database will be located within a secure password-protected network on a secure server managed by GRHANITE developers and the ACCESS team. Data will be processed within the database using various statistical software packages.

Data Management

The format and shape of the data to be extracted from each pathology laboratory varies, for example, some pathology laboratories store data as a wide data file including an individual's historical testing data, whereas some store data as a long data file with each test and accompanying result on a separate line. Data management personnel will map and convert data to a consistent format and shape and merge the data files. Each test type (see Table 2) will then be mapped to a disease

group, and data will be separated into disease-specific datasets for cleaning and management. Raw data will be converted to qualitative results where possible (negative, positive, and indeterminate). When quantitative results are provided for qualitative tests, pathology laboratories will be contacted to provide reference ranges. The dataset will then be restructured to represent 1 line per testing event to enable accurate test interpretation using case definitions. Duplicates and missing test result data will be excluded.

Analyses

Several important epidemiological indicators will be calculated utilizing data from pathology laboratory sites and are described in Table 2. Where appropriate, indicators will be stratified by sex (male and female) and age at time of test. Individuals with missing key demographic information (ie, sex or age) will be excluded from all analyses. Tests conducted within 7 days of each other will be considered a part of the same clinical encounter and, therefore, collapsed into the earliest visit date.

Where appropriate, pathology laboratory data will be appended to data collected from clinical services participating in ACCESS. The same indicators listed above will also be calculated; however, the expanded dataset will provide a more comprehensive description of STI and BBV testing, diagnosis, and management. Where possible, demographic data collected in clinical sites (such as sexual orientation or behavior and ethnicity, for example) will be linked to patients in pathology laboratory data to improve the characterization of individuals.

Table 2.

Indicator	Sexually transmitted disease / Blood-borne virus	Description
Total number of tests	All	The total number of tests conducted
Unique number of individuals tested	All	The total number of unique individuals that received at least one test
Test yield	All	The total number of positive results, divided by the total number of tests, expressed as a percentage
Proportion positive	All	The total number of unique individuals with a positive result, divided by the total number of unique individuals tested, expressed as a percentage
Repeat test for test of cure	Chlamydia	Test for chlamydia within six weeks of a previous positive test
Repeat test for reinfection	Chlamydia	Test for chlamydia at least six weeks after a previous positive test
Incidence	All	Among patients with at least two tests and whose first test result was negative, the number of unique incident cases divided by the total person time contributed by unique individuals who tested
Immunity	Hepatitis B virus	An anti- hepatitis B surface antibody titer measured as being >10mIU/L

External Use of Data

External researchers will be able to make data requests to access and utilize data collected in ACCESS. Applications will be considered by a central ACCESS coordinating committee and will require appropriate ethical approvals.

Ethical Approval

Ethical approval was provided by the Alfred Hospital Ethics Committee (Project No. 90/12 and Project No. 248/17). Individual consent is not collected in this study, in line with national standards [32].

Results

To date, over 20 million STI and BBV laboratory test records have been extracted for analysis for surveillance monitoring nationally. Recruitment of laboratories is ongoing to ensure appropriate coverage for each state and territory; reporting of indicators will occur in 2019 with publication to follow.

Discussion

ACCESS is a novel and innovative surveillance system that provides important data that can be used to understand trends in case reporting and monitoring the uptake and outcomes of testing for STIs and BBVs in Australia.

Strengths

There are several key strengths to the ACCESS pathology laboratory sentinel surveillance system. First, the use of specialized software enables the anonymous linkage of individuals between pathology laboratories and clinical sites. We are unaware of any similar STI or BBV surveillance system that has the capacity for such broad data linkage internationally. The capacity for data linkage across services and service types is particularly important, given that people may access multiple services for testing and management of STIs and BBVs [33,34]. The extent of use and the crossover of attendance at multiple services and service types is not known in Australia, and analysis of service-specific data is likely to underascertain service utilization and disease incidence in many risk groups. Second, some STIs—notably chlamydia—are most commonly diagnosed in general primary care services, undermining the potential to recruit a representative sample of sentinel clinical sites. Coverage via pathology laboratory data is a more effective and efficient way of monitoring these infections. Third, data collected in pathology laboratory sites have broad utility in monitoring disease incidence and prevalence as well as monitoring cascades of care by tracking individuals' progression from diagnosis through ongoing care. For example, follow-up

of an individual with an HIV diagnosis can be observed using the HIV viral load test records that follow. If the individual's viral load reaches below a particular threshold, it is an indication that the individual is on treatment and is no longer able to transmit HIV. Data can also be linked to additional datasets in clinical services that provide enhanced information on service utilization and membership of priority populations. Finally, because of flexibility of the data extraction system, it is possible to add additional tests to the pathology laboratory extraction with minimal resources, if this is required by the Departments of Health in the future.

Limitations

Some limitations to the system should be considered. First, we are unable to determine if the first identified case of a chronic infection (such as HIV, HBV, or HCV) is the date of diagnosis, as an individual may have first tested positive before 2009 (the earliest date of data extraction), and thus a positive test may not represent a new diagnosis. However, a pilot is underway to link the ACCESS pathology laboratory data to Australian BBV passive surveillance systems to help resolve this issue. Second, a significant amount of STI and BBV testing in Australia occurs in private pathology laboratories and not all private pathology laboratories currently participate in ACCESS. However, sentinel surveillance systems are not intended to capture all testing or positivity data, rather they should provide a representative sample of the population of interest. The representativeness of the system has not been established; however, geographical visualization of pathology laboratory collection sites (see Figure 1) suggests that there is reasonable coverage across urban and regional areas of Victoria and New South Wales. Furthermore, the anticipated linkage to passive surveillance data will help assess the representativeness of those being diagnosed with an STI or BBV. Finally, other than chlamydia, STIs and BBVs are concentrated in priority populations, defined by sexual identify, ethnicity, or risk practices (such as injecting drug use)—information that is not routinely collected by pathology laboratories. ACCESS is currently exploring ways to identify these populations in pathology laboratory data. For example, ACCESS collaborators recently analyzed data from a semiautomated sentinel surveillance system that preceded ACCESS in Victoria [35] to explore the potential of using testing pattern data to identify gay and bisexual men who have sex with men in STI surveillance systems. It was found that if an individual was identified as ever having an anorectal swab (for chlamydia or gonorrhea testing), it was a highly predictive and valid marker of gay and bisexual men who have sex with men attending sexual health clinics [36]. Additional predictive algorithms to identify priority populations will be investigated and validated in ACCESS pathology laboratory and clinical sites. For example, pregnant women receiving antenatal screening could be identified through concurrent rubella, syphilis, and HBV testing and people from culturally and linguistically diverse communities could be identified through the use of electronic ethnicity classification software [13,14].

Conclusions

The ACCESS pathology laboratory sentinel surveillance network is a unique surveillance system that collects data on regular diagnostic testing and linkages to and retention in care. Its initial implementation as a chlamydia surveillance system provided a platform from which the system can be expanded. This system can inform the development of surveillance systems globally to measure progress made toward reaching both local and global targets for reducing the impact of STIs and BBVs.

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Conflicts of Interest

MH received support from Gilead Sciences, Abbvie, and BMS for investigator-initiated research. All other authors declare that they have no competing interests.

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Abbreviations

ACCESS: Australian Collaboration for Coordinated Enhanced Sentinel Surveillance
BBV: blood-borne virus
HBV: hepatitis B virus
HCV: hepatitis C virus
STI: sexually transmitted infection

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Protocol

Development of a Caregivers' Support Platform (Connected Health Sustaining Home Stay in Dementia): Protocol for a Longitudinal Observational Mixed Methods Study

Estefania Guisado-Fernandez[1], MD; Brian Caulfield[1], PhD; Paula Alexandra Silva[2], PhD; Laura Mackey[3], PhD; David Singleton[4], BA; Daniel Leahy[4], BA; Sébastien Dossot[4], BA; Dermot Power[5], MD; Diarmuid O'Shea[6], MD; Catherine Blake[3], PhD

[1]Insight Centre for Data Analytics, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Dublin, Ireland
[2]DigiMedia Research Center, Universidade de Aveiro, Aveiro, Portugal
[3]School of Public Health, Physiotherapy and Sports Science, University College Dublin, Dublin, Ireland
[4]Applied Research for Connected Health, University College Dublin, Dublin, Ireland
[5]Medicine for the Older Person, Mater University Hospital, Dublin, Ireland
[6]Department of Geriatric Medicine, St. Vincent's University Hospital, Dublin, Ireland

Corresponding Author:
Estefania Guisado-Fernandez, MD
Insight Centre for Data Analytics
School of Public Health, Physiotherapy and Sports Science
University College Dublin
Belfield University Campus
Dublin, D4
Ireland
Phone: 353 0838345003
Email: estefaniaguisadofernandez@gmail.com

Abstract

Background: Dementia disease is a chronic condition that leads a person with dementia (PwD) into a state of progressive deterioration and a greater dependence in performing their activities of daily living (ADL). It is believed nowadays that PwDs and their informal caregivers can have a better life when provided with the appropriate services and support. Connected Health (CH) is a new technology-enabled model of chronic care delivery where the stakeholders are connected through a health portal, ensuring continuity and efficient flow of information. CH has demonstrated promising results regarding supporting informal home care and *Aging in Place*, and it has been increasingly considered by researchers and health care providers as a method for dementia home care management.

Objective: This study aims to describe the development and implementation protocol of a CH platform system to support informal caregivers of PwDs at home.

Methods: This is a longitudinal observational mixed methods study where quantitative and qualitative data will be combined for determining the utility of the CH platform for dementia home care. Dyads, consisting of a PwD and their informal caregiver living in the community, will be divided into 2 groups: the intervention group, which will receive the CH technology package at home, and the usual care group, which will not have any CH technology at all. Dyads will be followed up for 12 months during which they will continue with their traditional care plan, but in addition, the intervention group will receive the CH package for their use at home during 6 months (months 3 to 9 of the yearly follow-up). Further comprehensive assessments related to the caregiver's and PwD's emotional and physical well-being will be performed at the initial assessment and at 3, 6, 9, and 12 months using international and standardized validated questionnaires and semistructured individual interviews.

Results: This 3-year funded study (2016-2019) is currently in its implementation phase and is expected to finish by December 2019. We believe that CH can potentially change the PwD current care model, facilitating a proactive and preventive model, utilizing self-management–based strategies, and enhancing caregivers' involvement in the management of health care at home for PwDs.

Conclusions: We foresee that our CH platform will provide knowledge and promote autonomy for the caregivers, which may empower them into greater control of the care for PwDs, and with it, improve the quality of life and well-being for the person they are caring for and for themselves through a physical and cognitive decline predictive model. We also believe that facilitating information sharing between all the PwDs' care stakeholders may enable a stronger relationship between them, facilitate a more coordinated care plan, and increase the feelings of empowerment in the informal caregivers.

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KEYWORDS

connected health; dementia; caregivers; home care; home monitoring

Introduction

Background

Dementia is a neurodegenerative chronic condition that is frequently described as a clinical syndrome characterized by cognitive and functional decline accompanied by changes in a person's behavior and personality, which interferes with social or occupational functioning [1]. As the World Health Organization (WHO) reports, an estimated 47 million people worldwide were affected in 2015, and these numbers are expected to increase to 75 million by 2030 and 132 million by 2050 [2]. This was one of the main reasons for the WHO to designate dementia as a public health priority in 2012 [3], launching a public health dementia plan in 2017 [2]. Dementia is considered one of the most disabling chronic diseases that leads the person with dementia (PwD) into a state of progressive deterioration and a greater dependence in performing their activities of daily living (ADLs).

A dementia diagnosis also has a significant impact on the PwD's family who often bear the responsibility of caring for them as their condition progresses. Family members, usually a spouse or a child, are often referred to as *informal caregivers*, as they provide unpaid and continuous assistance contrary to formal caregivers who are paid for their professional services [4]. Informal caregiving can help to maintain the PwD at home, avoiding institutionalization and providing the *Aging in Place* new model of care, which consists of helping older people to remain living at home for as long as possible; avoiding nursing home placement; and contributing to an increase in well-being, independence, social participation, and healthy aging [5]. However, along with the well-being and economic improvement that *Aging in Place* can offer, previous research has also shown that the majority of people older than 75 years prefer living independently at home for as long as possible [6].

Although it is recognized that dementia can bring many challenges for the PwDs and their caregivers, it is also believed that nowadays they can have a better life when provided with the appropriate diagnosis and the proper services and support [7]. Connected Health (CH) is a new technology-enabled model of chronic care delivery where the stakeholders are *connected* through a health portal, ensuring continuity and efficient flow of information [8]. CH has demonstrated promising results regarding supporting informal home care and *Aging in Place* [9,10]. It represents an opportunity for passive and unobtrusive home monitoring, and increasingly, it is being considered by researchers and health care providers to be an enabler for dementia home-based health and wellness measurement and monitoring using mobile devices for storage, update, and transmission of patient data. The data captured from everyday life in PwDs can be of great value when put in the hands of the appropriate stakeholders, such as the health care professionals and the informal caregivers, as it can help to track the progress of PwDs and act as a predictor of any cognitive or physical decline [11]. Furthermore, reductions in PwD's caregiver burden, stress, depression, and anxiety as well as improved self-efficacy and confidence regarding caregiving skills have also been found; hence, it is believed that these results can be extrapolated to PwDs and that the implementation of these technologies may then improve the quality of life for both the PwD and their caregiver [12].

In terms of technology-driven interventions for dementia care, recent research shows that CH can improve various aspects of informal caregiving, such as confidence, depression, and self-efficacy, through the provision of multiple components personalized to each individual. In addition, informal caregivers can benefit from the interaction with other peers or health care professionals [13]. Focusing on the informal caregiver support provided, we found multiple types of technologies in the literature that can be categorized under the umbrella term of CH, including assisted living technology or ambient assisted living technologies, information and communication technology, smart homes, telehealth, telemonitoring, mobile health, and electronic health. Their purpose is to support the informal dementia caregiver in the physical, emotional, and social spheres of their role. As a result, the main outcome of interest of the studies where these technologies are used was an improvement in caregiver's mental and physical well-being, comparing before and after deployment, as measured by caregiver's stress, anxiety, depression, burden, and quality of life [14]. A systematic review conducted by Godwin et al [14] on technology-driven interventions for caregivers of PwDs found that these interventions showed positive results in the potential reduction of the caregivers' burden, improvement in their mental health, increase in their caregiving skills, and increase in competence as a direct benefit from online education, internet-based support groups, computer-mediated interactive voice response systems, and online skill building [14]. This is in line with the current trends of digital interventions for facilitating patients' and caregivers' empowerment [15-17]. Another reason for this growing interest for CH in supporting dementia home management is that it can offer a cost-effective alternative to

face-to-face care, and it has been progressively integrated into hospitals, physician's offices, patient homes, and other settings. At the same time, it allows access to personalized health education and support for self-management [18].

A good example found in the literature using a combination of patient home monitoring and informal caregiver support is the ALADDIN (Assisted living of Dementia elDerly INdividuals and their carers) project, which was conducted by Torkamani et al in 2014 [12]. ALADDIN is a computerized platform designed to offer support and information to the carer. It also manages and communicates information related to the PwD and their carers from their home to the clinicians, facilitating distant monitoring. It was tested in a multisite randomized controlled pilot study with 30 community-living informal caregivers of PwDs. The intervention and control groups were assessed at baseline and at 3 and 6 months in terms of burden, depression, and quality of life for the caregiver and in terms of cognitive and disease stage, functional disability, comorbidities, and quality of life for the PwD. The authors reported a significant improvement in the quality of life of the carers in the platform group, with some reduction in carer burden and distress, and that the platform was useful in monitoring the patients and facilitating contact with other professionals. In addition, carers and clinicians rated the access to and use of the ALADDIN platform positively. The success of studies such as this supports further testing of the utility and value of CH in other dementia cohorts and for longer periods and investigating the impact that it can have in the care of PwDs.

Study Aim

This paper describes the development and implementation protocol of a CH platform system to support informal caregivers of PwDs at home. We believe that a better understanding and more involvement in dementia home care can improve the informal caregivers' caring experience along with their quality of life and well-being. We want to explore if CH can offer additional support to traditional home care, promoting PwD and caregiver well-being and reducing the amount of burden and stress experienced by the caregiver, which may be translated into better care coping. In addition, we want to gain an understanding of the potential barriers and enablers to adoption by PwD and their informal caregivers of a CH platform to uncover how to change potential negative attitudes toward technology (behavioral change).

Methods

Study Design

This paper reports the protocol for a project based on a pilot study conducted by Applied Research in Connected Health, University College Dublin (UCD), between March and June 2014, where technology was deployed to 28 PwD and caregiver dyads for 6 weeks. The pilot project implemented a CH model prototype into dementia home care to investigate its feasibility and acceptability among PwDs and their informal caregivers. The following home-monitoring devices were deployed in the participants' homes for monitoring the PwD (Multimedia Appendix 1): an Omron blood pressure (BP) monitor (Omron Healthcare, Kyoto, Japan), a Withings Pulse activity tracker (Withings consumer electronics, Paris, France), a Withings scale (Withings consumer electronics, Paris, France), a ResMed Sleep Minder (Biancamed Ltd, Dublin, Ireland), and an Android tablet with the online health platform where all the data collected from the monitoring devices were uploaded and made available for the informal caregivers and the PwD's health care professionals. Furthermore, the health platform included a section with dementia disease information videos, an online diary section, and a questionnaires section where informal caregivers could periodically fill out some questionnaires regarding the PwD's ADLs. During the course of the development, the researchers communicated with PwDs and caregivers via video conferencing using the Android tablet provided. Further comprehensive assessments were conducted before and after the CH devices deployment for measuring the informal caregivers' and PwDs' quality of life, stress, and depression using scientifically validated questionnaires. Participants were recruited from 2 university hospitals in Dublin that work in collaboration with UCD. Results from its implementation and evaluation in terms of usability and user experience were used to develop the longitudinal project study design that is explained next.

The knowledge acquired from the literature review and the pilot study was applied in the design and development of *Connected HEalth Sustaining home Stay in Dementia* (CHESS), a longitudinal observational mixed methods study where quantitative data will be combined with qualitative data for determining the utility of a CH platform for dementia home care. For this purpose, 3 main objectives have been defined: (1) project feasibility—to evaluate the effectiveness of the CH platform in supporting caregivers of PwDs compared with usual care and caregivers' ability to cope; (2) impact of CH in dementia home care—in terms of the PwD and their informal caregivers' physical and mental health, quality of life, and well-being; and (3) users' feedback—to determine the CH platform's usability and user experience from the caregivers' perspectives.

Participants: Inclusion and Exclusion Criteria

Dyads consisting of a PwD and their informal caregiver living in the community are eligible for this study. For inclusion, the PwD must have a confirmed diagnosis of dementia by a health care professional, have a Mini-Mental State Examination (MMSE) score of 10 or above, have a live-in or dedicated informal caregiver (living with the PwD or spending with them at least 5 days a week, with no minimum hours per day requirement), be 65 years or older, be fluent in English (verbally and written), have a life expectancy of more than 6 months with no hospital admissions in the 3 months before enrolment, have adequate hearing and vision, and not be actively involved in another research study.

Caregivers must be live-in or dedicated informal caregivers, be fluent in English (verbally and written), have adequate hearing and vision, have a life expectancy of more than 6 months, and not be involved in another research study.

In case of not having an internet connection at home, it will be provided to the participants. Therefore, this has not been considered as a selection criterion.

Ethical Approval, Participants' Recruitment, and Seeking Consent

Ethical approval from the participating hospitals where recruitment will take place has been granted. Informed consent will be obtained on an individual basis in accordance with legal and ethical guidelines, following careful explanation and provision of an informed consent form for the PwD and a separate informed consent form for the caregiver, detailing their level of involvement. This provided informed consent and cognitive status will be reviewed before each quarterly assessment, giving the PwD and their informal caregiver the right to withdraw at any time. In case the cognitive status decreases under the minimum inclusion score of 10 points or their health declines significantly, they will be asked to abandon the study.

Intervention Description

This will be a longitudinal cohort study with 2 groups: the *intervention group*, which will receive the CH technology package at home, and the *usual care* group, which will not have any CH technology package at all. Selection to the CH or usual care group will be made by the PwD and their informal caregiver; thus, we will have adopter (intervention) and nonadopter (usual care) groups. The volunteer PwD-caregiver dyads will freely choose in which group they would like to participate as we acknowledge that this is a vulnerable population at an advanced age who might not be technology educated or might not feel comfortable with technology.

The CH technology package (Multimedia Appendix 2) consists of an online health platform designed for the informal caregiver that runs in a tablet computer (Samsung Galaxy Tab A 10.1, 2016) connected to a range of PwD monitoring devices for home use, including a BP monitor (Omron M6), an electronic weighing scale (Withings), and an activity and sleeping tracker (Withings Go). The online platform includes 4 sections (Multimedia Appendix 3). The first (Multimedia Appendix 4) consists of an information and resource section that provides access to website links and videos from Irish dementia experts with reputable information regarding dementia management and helpful advice about daily home care. The second section (Multimedia Appendix 5) provides daily and weekly questionnaires that gather health-related information about the PwD, that is, mood, nutrition, activity, bowel movements, and medication compliance, which are completed by the caregiver and viewed by the health care professionals involved in the PwD's care. In addition, questionnaires for the informal caregivers are included to assess their own health and well-being, that is, mood, energy levels, sleeping quality, and anxiety levels. This will be used for research purposes only and not viewable for health care professionals. The third section (Multimedia Appendix 6) includes a journal to be used as an online diary where the informal caregivers can maintain recordings of events, and it also contains summary reports of changes in the PwD care plan provided by the health care professionals from previous consultations. The fourth section (Multimedia Appendix 7) offers a dashboard for the caregivers and health care professionals to view the PwD activity levels, sleep patterns, BP, and weight, recorded by the monitoring devices provided along with the health platform. During the deployment, the informal caregiver has access to the health platform at any time using the tablet computer. They will have to measure the PwD's BP once a week and input the results into the *measurements* section. Safety range values of each individual BP will be set up in the health platform during the first assessment, so this measurement will act as their reference BP value. If BP measurements fall outside these parameters (2 points above or below the first assessment values), a message will pop up on the tablet screen advising the informal caregivers to check how the PwD is feeling at that moment and to take another BP measurement in 30 min. Following this, if the value measured is still outside the normal limits and the PwD is feeling unwell, they will be advised to contact their general practitioner. Weight has to be measured by the informal caregiver once a month and will be automatically uploaded from the scale to the health platform via Wi-Fi. Daily activity and sleeping, tracked from the activity wrist tracker, is automatically uploaded via Bluetooth into the health platform. In addition, the informal caregivers will be prompted through messages under each section name to complete the daily and weekly questionnaires on the platform, to take the weight and BP, and to have a look at the information section, which will be updated with new resources regularly.

The encrypted online platform will securely connect all the key stakeholders involved in the PwD's care (ie, informal caregiver, general practitioner, public health nurse, and hospital geriatric services). As mentioned above, the generated data will be presented in the platform and made available for the informal caregivers and the health care professionals as an objective measure of the patient's health status.

Outcomes Measurements

A multidimensional profile of the well-being of caregivers and PwDs will be tracked longitudinally over the duration of the study, with some brief measures recorded daily (questionnaires and PwD's activity and sleeping), another weekly (BP) or monthly (weight), and others at quarterly intervals (assessments questionnaires). These measures will be contrasted between the intervention and usual care groups at discrete time points and over time. The daily and weekly monitoring will consist of simple Likert-type questions about the PwD and caregiver (completed by the caregiver) along with the physical activity of the PwD measured in steps and sleep duration.

More detailed outcomes will be compared and evaluated through international validated questionnaires administered by the researcher and that are commonly used in the clinic to measure well-being. Choosing the appropriate questionnaires and the right time for completing them was decided after a concise literature review that also required meetings and advice from experts in dementia and considerations of the demands on the caregiver and PwD. Our outcome domains can be divided into 2 groups that are described below (Multimedia Appendix 8). In addition, qualitative interviews will take place at months 3 and 9 of the year of deployment to analyze caregivers' satisfaction with the CH platform along with the usability and user experience.

Person With Dementia–Related Outcomes

The cognitive status level in the PwD will be measured using the *Mini-Mental State Examination* (MMSE) questionnaire. It is composed of 11 questions that cover 5 areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30, with a score of 23 or less being indicative of cognitive impairment. This is a quick and easy tool to administer directly to the PwD and is very useful when having to conduct it repetitively [19,20].

Behavioral and neuropsychiatric symptoms will be assessed with the short version of the *Neuropsychiatric Inventory Questionnaire* (NPI-Q). It is a way of providing a brief assessment of the PwD's neuropsychiatric symptoms, which has been seen to be sensitive and reliable to capture changes in time related to delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, aberrant motor behavior, sleep and night-time behavior disorders, and appetite and eating disorders. It is based on responses of the caregivers who must also rate these symptoms in terms of frequency (how frequent those symptoms occur), severity (how severe and how much it affects the PwD), and distress (how distressing is it for them as caregivers and how much it may affect them). The NPI-Q does not have a cutoff score and, therefore, does not have a numeric scoring. Each domain is scored for frequency, severity, and associated caregiver distress, and the interviewer has to analyze them in those given terms [21-23].

Quality of life will be measured with the *Dementia Quality of Life* (DEMQOL) questionnaire, to gain an insight into their health-related quality of life. This is designed to work across dementia subtypes and care arrangements and is suitable for all the stages of the disease. It is composed of 2 questionnaires: (1) DEMQOL, a 28-item questionnaire answered by the PwD (self-reported quality of life) and (2) DEMQOL-Proxy, a 31-item questionnaire answered by the caregiver (PwDs' caregiver-reported quality of life). Scored items are summed to produce a total score, with higher scores meaning a better health-related quality of life [24,25].

Anxiety and depression levels will be examined using the *Hospital Anxiety and Depression Scale* (HADS), a simple and brief self-reported questionnaire. A total summary score classifies the respondent into 3 groups, depending on their levels of depression and anxiety, into normal, borderline case, or abnormal. This questionnaire does not provide a diagnosis as it was created for screening purposes only [26,27].

PwD functional levels will be assessed with the *Disability Assessment for Dementia* questionnaire, designed for community-based individuals with Alzheimer dementia type, but it has been used in other types of dementia research more recently. It is a tool used by health care professionals to investigate the PwD levels of dependency and to guide the provision of tailored interventions for PwD. In addition, as a research tool, it can be used to describe the functional characteristics of the PwD and the progression of the disease. A total score is converted out of 100, with the result of a percentage that gives an understanding of the PwD global function in ADLs. Higher scores mean less disability in conducting ADLs, with lower scores indicating more dysfunction and more dependency on the caregiver [28].

PwD frailty will be examined with the *Survey of Health, Ageing, and Retirement in Europe Frailty Instrument (SHARE-FI)*. It is a 5-item validated scale created by Romero-Ortuno et al [29,30], which predicts frailty and mortality in primary care similarly to a frailty index based on a comprehensive geriatric assessment. It is quick and easy to administer as it only requires 5 simple measurements to be entered in an open-access online calculator, which we have incorporated into our health platform.

PwDs' risk of falls; gait, and mobility assessment will be conducted with *Kinesis Quantitative Timed Up and Go (QTUG*). It is an online app tool for the QTUG test, validated through research by the company *Kinesis* that measures different phases of the *Timed Up and Go* test [31]; time in turning; and reflects overall locomotor task ability, variability, and stability. QTUG can identify a large range of temporal gait parameters. Using an internal algorithm integrates these with clinical falls risk indicators to calculate a falls risk score [32,33].

Caregiver-Related Outcomes

Quality of life in the caregiver will be measured using the EuroQol-5 dimention-5 level instrument (*EQ-5D-5L*) [34]. It is a standardized measure of health status, creating a simple descriptive profile and a single index value that can be used for the clinical and economic evaluation of health status and health care. It consists of 2 parts. The first part is the descriptive system that comprises 5 dimensions, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of these having 5 possible response options: no problems, slight problems, moderate problems, severe problems, and extreme problems. The interviewee must choose 1 answer that best represents their health state. The second part is the visual analogue scale (EuroQol group Visual Analogue Scale, EQ-VAS), which is a 20-cm vertical scale scoring from 0 to 100, with endpoints marked with "the best health you can imagine" for the 100 score and "the worst health you can imagine" for the 0 score. The interviewee has to mark out a point in the scale, providing a score representing their self-rated score. From the first part, an individual health state is defined for each respondent combining 1 level from each of the 5 dimensions, giving a personalized digit code for their health status. The second part, the EQ-VAS, provides a quantitative measure of the interviewed health status.

Anxiety and depression levels will be assessed using the same tool as applied for the PwD, the HADS, which is described above.

The burden of care and ability to cope will be estimated using the *Zarit Burden Interview questionnaire*. It is composed of 22 questions about the impact of the PwD's disabilities in the caregiver's life and has been designed to reveal the stress experienced by the caregiver. For each item, the caregivers must indicate how burdened they are (never, rarely, sometimes, quite frequently, or nearly always). A total score can be calculated from the summing of each answer, with higher scores indicating higher levels of burden and stress because of the caring process [35,36].

Caregiver sleep quality will be examined with the *Pittsburgh Sleep Quality Index*, designed to evaluate the overall sleep quality for 1 month. It is a 19-item self-reported questionnaire with 7 subcategories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. This questionnaire was initially created to measure the sleeping quality in psychiatric populations but has been widely used for clinical and research purposes [37,38].

Caregivers' satisfaction with the platform and usability of the system will be investigated via semistructured individual interviews conducted before and after the technology deployment, with the support of a previously designed interview guide that includes the following topics: (1) reason for participating in the project; (2) platform feedback on usability, usefulness, helpfulness, expectations, suitability, and improvements; (3) caregivers' impressions of PwD perceptions of the CHESS platform; and (4) caregivers' perceptions of home care technology in general. The interviews will be audio recorded for later transcription and analysis.

Timing of Measurements

In both groups, PwD-caregiver dyads will be followed up for 12 months during which they will continue with their traditional care plan, but in addition, the intervention group will receive the CH package for their use at home during 6 months (months 3 to 9 of the yearly follow-up), thus enabling a baseline phase, intervention phase, and a postintervention phase to be delineated. During the initial assessment (month 0), PwDs' past medical history and PwDs' and informal caregivers' social history and demographic data will be obtained. Further comprehensive assessments related to the caregivers' and PwDs' emotional and physical well-being will be performed at the initial assessment and at 3, 6, 9, and 12 months using the international and standardized validated questionnaires explained above. They will be completed electronically on the researchers' administrators interface of the health platform by the caregiver and the patient, with the help of the researchers (see Table 1 for the comprehensive list of questionnaires and their timing during the 12 months follow-up, and see Multimedia Appendix 8 for a screenshot of the administrators' interface view of the questionnaires). Respondent burden is a key consideration, and so in this way, all in-depth questionnaires are reserved for quarterly face-to-face interviews with the researchers, whereas daily and weekly questionnaires modules with which the caregiver interacts independently through the user interface are kept short and simple.

Table 1. Quarterly assessments and timing with the caregiver and person with dementia during the yearly follow-up.

Participant	Month 0	Month 3	Month 6	Month 9	Month 12
PwD[a]	Past medical history, vital signs; DEMQOL[b], HADS[c], MMSE[d], QTUG[e]; Frailty (SHARE-FI[f]), DAD[g], DEMQOL, proxy, NPI-Q[h]	DEMQOL, HADS, MMSE, QTUG, Frailty (SHARE-FI), DAD, DEMQOL proxy	DEMQOL, HADS, MMSE, QTUG, Frailty (SHARE-FI), DAD, DEMQOL proxy, NPI-Q	DEMQOL, HADS, MMSE, QTUG, Frailty (SHARE-FI), DAD, DEMQOL proxy	DEMQOL, HADS, MMSE, QTUG, Frailty (SHARE-FI), DAD, DEMQOL proxy, NPI-Q
Caregiver	EQ-5D-5L[i], HADS, IPAQ[j], NVS[k], PSQI[l], ZBI[m]	EQ-5D-5L, HADS, NVS, PSQI, ZBI	EQ-5D-5L, HADS, IPAQ, NVS, PSQI, ZBI	EQ-5D-5L, HADS, NVS, PSQI, ZBI	EQ-5D-5L, HADS, IPAQ, NVS, PSQI, ZBI

[a]PwD: person with dementia.

[b]DEMQOL: Dementia Quality of Life.

[c]HADS: Hospital Anxiety and Depression Scale.

[d]MMSE: Mini-Mental State Examination

[e]QTUG: Quantitative Timed Up and Go.

[f]SHARE-FI: Survey of Health, Ageing, and Retirement in Europe Frailty Instrument.

[g]DAD: Disability Assessment for Dementia.

[h]NPI-Q: Neuropsychiatric Inventory Questionnaire.

[i]EQ-5D-5L:EuroQol group-5 dimension- 5 level questionnaire.

[j]IPAQ: International Physical Activity Questionnaire.

[k]NVS: Newest Vital Signs.

[l]PSQI: Pittsburgh Sleep Quality Index.

[m]ZBI: Zarit Burden Interview.

Initial Users' Evaluation

A first model of the CH platform was developed over 12 months. Once the first stage of development of the platform was completed, we decided to conduct various levels of user testing with researchers and clinicians from our group to detect any possible platform failures or bugs, to verify that it worked according to our expectations, and to redefine the user interface based on their findings. During February 2017, 5 researchers and clinicians used the technology for 1 week, completing the tasks as the caregiver would and, also, wearing the activity tracker 24/7 as the PwD would. They were encouraged to think and to use the platform as a caregiver would and were provided with a list of the tasks to be completed during the week, that is, to measure their weight and to measure their BP at least once, to have a look at the information section (to watch some videos and to access some of the websites' links provided), to write down minimum 1 entry in the journal, and to have a daily look

at their activity and sleeping, so as to ensure that the devices were accurately syncing and being presented accurately in the measurements section. A log was created specifically for them to record any potential issues that appeared during the platform and device use, with the idea of solving them before the deployment phase. The platform seemed to work according to our scheme, and devices were syncing appropriately. Data were showed in the measurements section, and videos and links from the resources section were working properly. Researchers feedback was used to make some small changes in the platform's look to give it a clearer and cleaner aspect and make it easier to use.

Data Analysis

Quantitative data from the participants' quarterly assessments and daily monitoring data will be exported from the platform in the form of Excel documents. Descriptive statistics will be used to summarize the initial demographic data from our sample, which are obtained from the medical notes and the initial assessment examination (month 0), and for describing the findings of the questionnaires at each assessment point (months 3-12). Exploratory factor analysis will be conducted on the measured variables to identify the main constructs in our sample and how they correlate and interact with each other.

The main data collection points will be at 2 stages: months 0 and 12, as they will give us insight into the progress of the disease and the quality of life of the PwD and caregivers over 1 year, whereas interim data points will be available at 3, 6, and 9 months. Thus, the primary analysis of these repeated measures within each individual will be assessed using linear mixed models (LMMs). LMMs are suitable for correlated data such as these, and random intercepts and slopes can be allowed for individuals and subgroups. Change over time will be assessed, and differences between subgroups and interactions between covariates will be explored.

We also want to investigate changes in the scores between each assessment point (at 0, 3 6, 9, and 12 months). For this, analysis of variance or the equivalent nonparametric tests will be used. Regarding the assessments at months 3 to 9, these are the months when the technology is deployed at their homes and in which we can assess any potential impact derived from its use between the intervention and the usual care groups. This group comparison will be estimated by comparing the change in the volunteers' scores between those 2 assessments (month 3 and month 9) using *t* tests or the correspondent nonparametric tests when appropriate.

For this, a sample size calculation was derived using a rule of thumb for 20 observations for each dependent variable, so a sample size of 60 PwD-caregiver dyads is proposed. For the comparison of outcomes between the intervention and the usual care groups, caregiver burden and quality of life will be the primary outcome measure assessed at enrollment and at 6 and 12 months. Acknowledging that the PwD can deteriorate over time with a decline in their cognitive and functional status, we will use scores adjusted for baseline patient dependence and neuropsychiatric symptoms (analysis of covariance, ANCOVA model). We hypothesis a moderate between-groups effect size (d=0.5), so with 80% power and alpha=.05, a sample of 64 individuals in the intervention group and 64 in the usual care group is required for the *t* test. Adjusting for ANCOVA by sqrt (1-p2), where the p is the conservative correlation of 0.5 between repeated measures [39], results in a sample of 55 in each group. To account for dropout, 60 PwD-caregiver dyads will need to be recruited for each group. SPSS software (IBM Corp Version 24.0) will be used for this statistical analysis.

Analysis of the qualitative data obtained from the transcribed individual semistructured interviews will be analyzed using content analysis [40]. A guiding codebook will be used for this analysis, which will be created based on the topics examined in the interviews outlined above. The emerged categories will be organized, analyzed, and compared for generating themes. NVivo software version 12 for Macintosh (QSR International) will be used to organize the thematic analysis.

Results

This 3-year funded study (2016-2019) is currently in its implementation phase. It is expected to finish by December 2019, and preliminary data results are expected to be submitted for publication by mid-2019. We believe that CH care approach can potentially change our current care model, moving from a previous passive and reactive approach to a more proactive and preventive model, utilizing self-management–based strategies, and enhancing caregivers' involvement in the management of PwD's health care in the home.

Discussion

Principal Findings

With this mixed methods study, we are addressing 2 spheres in the dementia informal home care. One is the invaluable quantitative health data collected from the PwD daily monitoring and the fact that, although the informal caregivers play the main role in PwD home care, there are many inconsistencies regarding the support provided to them. On the other sphere, the literature suggests that despite current trends in research claiming a user-centered design for increasing adoption and use [41], PwDs are not sufficiently involved in the design and development of CH solutions for dementia home care. Therefore, PwDs' and their informal caregivers' needs and perspectives are not considered and integrated into the product designed, so they are not customized for them [42,43]. Consequently, because of the created necessity of understanding the needs and attitudes of PwD and their informal caregivers regarding CH technology, we have included a qualitative approach to address these deficits outlined here. We hope that our combined results from both domains, qualitative and quantitative, will bring new perspectives on how to design and conduct CH research with PwDs and their informal caregivers.

Conclusions

CH is emerging as a new approach to potentially change our current care model, moving from a previous passive and reactive approach to a more proactive and preventive model, utilizing self-management–based strategies, and enhancing caregivers' involvement in the management of PwD's health care in the home. In accordance with the *Chronic Care Model* [44], we

foresee that our platform will provide knowledge and promote autonomy in the caregivers, which may empower them into greater control of the PwD care and, with it, improve the quality of life and well-being for the person they are caring for and themselves through a physical and cognitive decline predictive model. We also believe that facilitating information sharing between the health care professionals and the informal caregivers may enable a stronger relationship between all the stakeholders, facilitate a more coordinated care plan, and increase feelings of empowerment in the informal caregivers.

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Conflicts of Interest

DS acknowledges change of employment as the product manager for Kinesis while being the information technology support for the CHESS project.

Multimedia Appendix 1
Applied Research in Connected Health, University College Dublin pilot project devices.
[PNG File, 129KB - resprot_v8i8e13280_app1.png]

Multimedia Appendix 2
Devices used for the Connected HEalth Sustaining home Stay in Dementia project.
[PNG File, 200KB - resprot_v8i8e13280_app2.png]

Multimedia Appendix 3
Caregivers' platform main screen.
[PNG File, 51KB - resprot_v8i8e13280_app3.png]

Multimedia Appendix 4
Information section.
[PNG File, 81KB - resprot_v8i8e13280_app4.png]

Multimedia Appendix 5
Questionnaires section.
[PNG File, 131KB - resprot_v8i8e13280_app5.png]

Multimedia Appendix 6
Profile section.
[PNG File, 59KB - resprot_v8i8e13280_app6.png]

Multimedia Appendix 7
Measurements section.
[PNG File, 79KB - resprot_v8i8e13280_app7.png]

Multimedia Appendix 8
Researchers' assessments interface.
[PNG File, 92KB - resprot_v8i8e13280_app8.png]

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Abbreviations

ADL: activity of daily living
ALADDIN: Assisted living of Dementia elDerly Individuals
ANCOVA: analysis of covariance
BP: blood pressure
CH: Connected Health

CHESS: Connected HEalth Sustaining home Stay in Dementia
EQ-5D-5L: Mini-Mental State Examination.
EQ-VAS: EuroQol group Visual Analogue Scale
HADS: Hospital Anxiety and Depression Scale
LMM: linear mixed model
NPI-Q: Neuropsychiatric Inventory Questionnaire
PwD: person with dementia
QTUG: Quantitative Timed Up and Go
UCD: University College Dublin
WHO: World Health Organization

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Protocol

Monitoring Immobilized Elderly Patients Using a Public Provider Online System for Pressure Ulcer Information and Registration (SIRUPP): Protocol for a Health Care Impact Study

Eugenio Vera-Salmerón[1,2,3], BSN; Claudia Rutherford[4], PhD; Carmen Dominguez-Nogueira[1], BSN; María Pilar Tudela-Vázquez[1,2], PhD; Victor J Costela-Ruiz[5], MHS; Basilio Gómez-Pozo[1,2,6], PhD

[1]Distrito Sanitario Granada-Metropolitano (Servicio Andaluz de Salud), Armilla, Spain

[2]Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Granada, Spain

[3]Unidades Asistenciales Churriana de la Vega y Peligros, Granada, Spain

[4]Beckett Senior Research Fellow Quality of Life Office, University of Sydney, Sydney, Australia

[5]Departamento de Enfermería, Facultad de Ciencias de la Salud, Universidad de Granada, Granada, Spain

[6]Unidad Interniveles de Prevención Promoción y Vigilancia de la Salud, Granada, Spain

Corresponding Author:
Basilio Gómez-Pozo, PhD
Distrito Sanitario Granada-Metropolitano (Servicio Andaluz de Salud)
Parque Tecnológico de la Salud, Edificio I+D Armilla, 2ª planta
Armilla,
Spain
Phone: 34 958 84 03 70
Email: basilio.gomez.sspa@juntadeandalucia.es

Abstract

Background: Pressure ulcers represent a major challenge to patient safety in the health care context, presenting high incidence (from 7% to 14% in Spain) and increased financial costs (€400-600 million/year) in medical treatment. Moreover, they are a significant predictor of mortality. The prevention of pressure ulcers in long-term care centers and patients' own homes is proposed as a priority indicator of health care quality. Early stage risk assessment and database recording are both crucial aspects of prevention, classification, diagnosis, and treatment.

Objective: This project proposes a 3-year study of immobilized patients residing in the Granada-Metropolitan Primary Healthcare District (DSGM) and monitored via the Pressure Ulcer Information and Registration System (SIRUPP, Spanish initials). The project aims to estimate the incidence of PUs among immobilized elderly patients, analyze the health-related quality of life of these patients by using the Pressure Ulcer Quality of Life (PU-QoL) instrument in a sample of 250 patients, determine the average time to complete wound healing, estimate the rate of pressure ulcers–associated mortality, and assess the predictive value of the Braden and Mini Nutritional Assessment risk measurement scales in a sample of 1700 patients.

Methods: The DSGM runs SIRUPP, which is linked to patients' electronic health records. Currently, 17,104 immobilized patients are monitored under this system. Health-related quality of life will be measured by patient self-reports using the Spanish Pressure Ulcer Quality of Life questionnaire, following cross-cultural adaptation and psychometric validation with respect to the English-language version.

Results: The project commenced in June 2017 and is expected to conclude in April 2020.

Conclusions: This study addresses two main health outcomes—the time needed for wound healing and the mortality associated with pressure ulcers—both of which might be accounted for by variations in clinical practice and the health-related quality of life of patients with pressure ulcers.

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KEYWORDS

primary health care; pressure ulcers; wound healing; health-related quality of life

Introduction

Background

Pressure ulcers (PUs) are injuries located in or under the skin, usually on a bony protrusion, resulting from pressure or shear forces [1,2]. They affect persons with reduced mobility and are associated with diverse health conditions and clinical settings. PUs may affect hospitalized patients, residents of nursing homes, the elderly, or persons living in their own homes, among others [3-7].

PUs represent a major public health problem, causing serious medical complications, severely reducing patients' health-related quality of life (HRQoL), and greatly increasing the financial costs of medical treatment [8]. Studies have reported a three-fold increase in mortality among hospitalized patients and an increase of 6.4 days in the length of hospital stay among patients with PUs. Consequently, the prevention of PUs in long-term care centers is considered a priority indicator of health care quality [9,10].

Most PUs are considered avoidable if suitable preventative measures are taken [11]. The three most important risk factors for PUs are mobility-activity, perfusion, and skin state [12]. Other risk factors include advanced age, long stay in care centers, medical history of PUs, diabetes, low blood pressure, sensory neuropathy, falls, kidney and peripheral vascular diseases, and nutritional status [7-9,11-13].

Estimates of the incidence of PUs worldwide have been determined. In Belo Horizonte (Brazil), an incidence of 5.7% was reported for a cohort of 442 hospitalized patients [14], while in Italy, a multicenter cohort study of 1083 hospitalized elderly patients reported an incidence of 22.7% [15].

The latest survey in 2013 by the Spanish Advisory Panel on Pressure Ulcers and Chronic Wounds reported that the prevalence of PUs varied from 7% to 8.5% in hospitals, 12% to 14% in nursing homes, and 8% to 9% among patients living at home; 65.6% of PUs were diagnosed during hospital stays or in nursing homes and 29.6% were diagnosed in home-care patients [16]. In the Granada-Metropolitan Primary Healthcare District (DSGM), which includes both urban and rural areas, the total immobilized patient population susceptible to the development of PUs is 16,467 (15% of persons aged≥65 years) [17]. According to the findings of the 4th National Study on PUs, for this population, the estimated prevalence of PUs would be 8%-9%, or 1300-1500 patients [16]. In total, the DSGM has 72 nursing homes for the elderly, with 4700 residents aged≥65 years. To record the incidence of PUs, the DSGM designed a specific instrument—the Pressure Ulcer Information and Registration System (SIRUPP, Spanish initials)—which has been integrated into patient electronic health records at the DSGM. SIRUPP has been presented, as a good practice initiative, to the EU Network on Patient Safety and Quality of Care [18]. It has been piloted in the DSGM and used as an instrument for clinical follow-up. The large number of immobilized patients currently registered in SIRUPP is expected to facilitate the follow-up stage of this research study.

The most commonly used tools to evaluate PU risk are the Braden scale and the Norton scale, although the latter does not consider the abovementioned risk factors. Accordingly, most research attention has been paid to the Braden scale and its psychometric properties [2,11,19]. Many factors representing the risk of PU development are omitted from this scale. Therefore, and in view of the known relationship between patient age and comorbidity, the Braden scale is not considered to offer high predictive performance for patients aged over 80 years [13]. For this reason, the parallel implementation of specific tests to evaluate the nutrition levels of these older patients has been recommended. Research evidence supports the use of the Mini Nutritional Assessment scale (MNA) to evaluate PU risk as a complement to the Braden scale. The MNA scale is a useful means of evaluating the nutritional status of elderly persons [9,20-24]. The MNA - Short Form questionnaire (MNA-SF) takes into account the subject's body mass index or the calf circumference, which is, perhaps, a more useful indicator for immobilized patients. For persons with cognitive impairment, the MNA test can be applied via an interviewer or relatives [25].

PUs can negatively impact the HRQoL [26]. A 1-year follow-up cohort study in Catalonia analyzed the factors associated with mortality and HRQoL in a sample of 1000 immobilized patients (mean age: 84 years), which included patients in a home-based health care program [27]. The study reported that comorbidity of PUs (measured by the Charlson index) was associated with a 14% higher risk of death. Stage I/II and III/IV PUs increased this risk by three and four times, respectively. When hospitalization exceeded 24 hours, mortality was 17% higher. On the contrary, a high self-perceived HRQoL (measured by the SF-12 health status questionnaire) and a low cognitive impairment were both associated with longer survival [28].

Patient-reported outcomes are of crucial importance in health care decision making [26,28]. To our knowledge, only one instrument has been specifically developed for patients with PUs, namely, the PU-QoL questionnaire [29,30].

From our literature review, we hypothesize that there is geographical heterogeneity in the incidence of PUs in the elderly. In addition, a high variability in clinical practice is expected, which will be expressed as heterogeneity in the time needed for the wounds to heal as well as differences in the mortality rates by place of residence. Furthermore, given the psychometric properties exhibited for some widely used questionnaires, it is expected that the MNA questionnaire on its own or in combination with the Braden scale will outperform the Braden scale as a predictive tool for the risk of PUs. Finally, we expect that the validation of the PU-QoL questionnaire in Spanish will preserve the psychometric properties of the original English version and allow for valid and precise estimation of the quality of life in patients with PUs.

Objectives

The objectives of this study were as follows:

1. To estimate the incidence of PUs in immobilized elderly patients:
   - To estimate the time to full wound healing

- To estimate the mortality associated with the presence of PUs
- To compare the responsiveness to change and the predictive value of the Braden and MNA questionnaires

2. To analyze the HRQoL of immobilized elderly persons with PUs
3. To translate, adapt, and validate the PU-QoL questionnaire in Spanish
4. To estimate patients' nutritional status (MNA-SF), cognitive status (the Reisberg Global Deterioration Scale) and functional independence (the Barthel scale)
5. To determine the PU-QoL questionnaire's ability to differentiate between clinical groups (eg, PU severity) and its responsiveness to change (eg, wound healing)

Methods

Design

This study is based on SIRUPP, which is a part of the patient electronic health record system in Andalucía. The system was designed by the SIRUPP study coordinator in 2015 to provide professionals with a standardized registration system for PUs and was initiated in 2017 as part of a proposed 3-year follow-up of immobilized patients, with no PUs at the outset. The SIRUPP system has been presented as a good clinical practice initiative to the EU Patient Safety and Quality of Care project. Among other aims, SIRUPP is intended to facilitate the evaluation of variations in clinical practice and participants' HRQoL. The incidence of PUs and the corresponding health outcomes will be assessed during the study, to be coordinated by the DSGM, located in the province of Granada (Spain). In Spain, primary health care districts are the main organizational public health structure for the planning, administration, and operational management of primary health services. Each district is structured into several primary health care zones (ZBS), each containing one or more health care centers. The DSGM contains 36 ZBSs and serves a population of 697,000 people. To achieve objectives 1 (incidence), 1-a (time elapsed until full wound healing), and 1-b (mortality), a pilot cohort study will be performed to monitor all immobilized patients registered in SIRUPP, presenting no PUs at the outset. The follow-up process will continue until the wound heals, the patient dies, or the project ends, whichever occurs first. To achieve objective 1-c (Braden and MNA questionnaires), we will conduct a repeated-measures prospective cohort study in a sample of immobilized patients without PUs registered in SIRUPP. With respect to HRQoL, objectives 2 and 3 will be addressed by means of a cross-sectional study in a sample of immobilized patients registered in SIRUPP. At this point of the project, patients who developed PUs since the start of the study will be recruited. Regarding objectives 4 (nutrition, cognition, and functional independence) and 5 (PU-QoL questionnaire), a repeated-measures cohort study (Tables 1 and 2) will be implemented for all immobilized patients registered in SIRUPP, who have developed PUs since the start of the study period.

Patients enter the SIRUPP registry as they fulfill the criteria established by the service portfolio in the Andalusian Health Service. Consequently, anybody who is at risk of impairment in their ability for moving, but not necessarily mobility-impaired at that time, is registered as *immobilized*. Therefore, the state of immobilization will be further categorized for all patients registered in SIRUPP by using the Braden mobility and activity subscales as well as the MNA-SF mobility subscale. This will provide additional up-to-date information on the actual state of patients' mobility. To minimize the underreporting of immobilized patients, periodic monitoring of compliance with management agreements at all health centers within the DSGM will be audited. Furthermore, variations in clinical practice may lead to a classification bias of PUs against other types of chronic wounds. To forestall this possibility, the project will include training in this respect for all nurses responsible for the care of immobilized patients. In addition, SIRUPP software incorporates a protocol for the evaluation and staging of chronic wounds that ensures homogeneous, standardized categorization in clinical practice. Finally, a fieldwork coordinator in charge of all follow-up activities will ensure that all the information obtained is up to date.

Table 1. SIRUPP Project CADENCE for immobilized patients without PUs.

Periodicity schedule	Day 0	Day 7	Day 14	Day 21	Day 28	After 90 days
Living at home						
Braden						
None/low risk	✓				✓	✓
Moderate/high risk	✓		✓		✓	✓
MNA-SF[a]	✓		✓		✓	✓
Living at nursing home						
Braden	✓	✓	✓	✓	✓	✓
MNA-SF	✓	✓	✓	✓	✓	✓

[a]MNA-SF: Mini Nutritional Assessment - Short Form.

Table 2. SIRUPP Project CADENCE for immobilized patients with PUs.

Periodicity schedule	Day 0	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Living at home						
MNA-SF[a], score						
12-14	✓					✓
8-11	✓		✓			
0-7	✓	✓				
Barthel	✓			✓		
GDS[b]	✓			✓		
PU-QoL[c]	✓			✓		
Living at nursing home						
MNA-SF, score						
12-14	✓		✓			
8-14	✓	✓				
0-7	✓			✓		
GDS	✓			✓		
PU-QoL	✓				✓	

[a]MNA-SF: Mini Nutritional Assessment – Short Form.

[b]GDS: Global Deterioration Scale.

[c]PU-QoL: Pressure Ulcer Quality of Life Questionnaire.

Participants

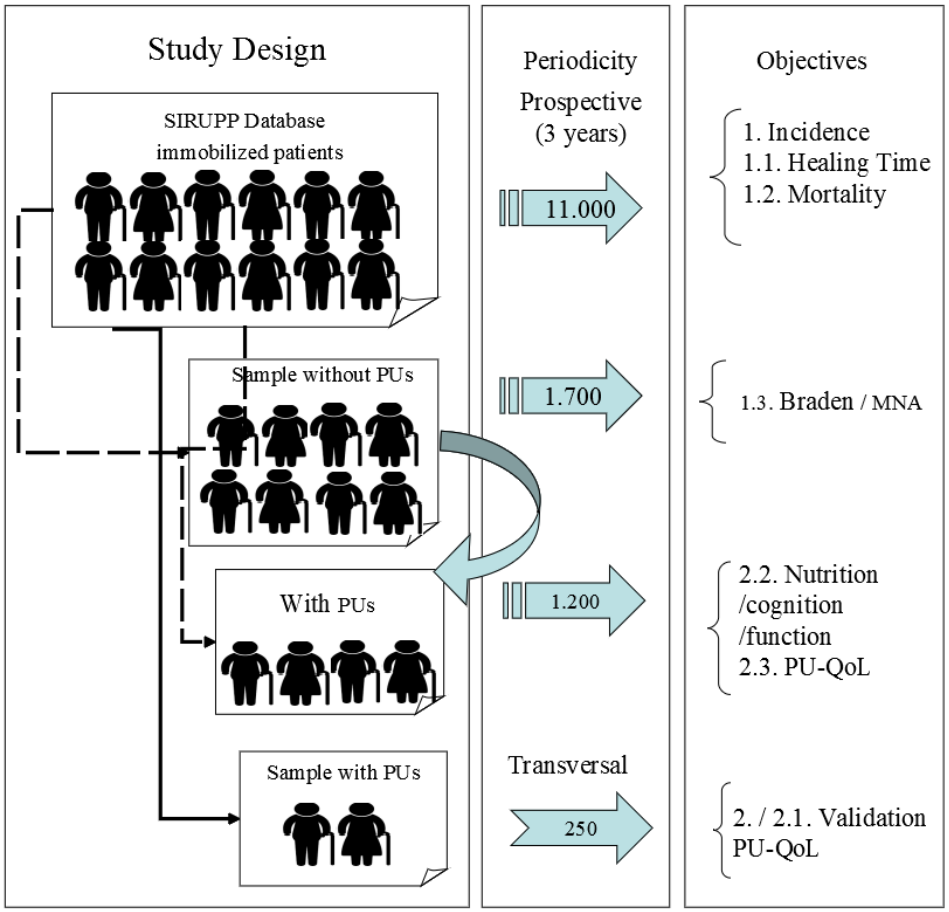
The inclusion criteria for patients are immobilized status, male or female gender, age≥65 years, living in their own home or a nursing home for the elderly, and receiving treatment at primary health care centers in the DSGM. Patients who understand the purpose of the study can provide informed consent to participate on their own. For patients with cognitive impairment, their legal guardians can understand the purpose of the study and provide informed consent.

Exclusion criteria are as follows: refusal to participate, patients with cognitive impairment that prevents them from understanding the purpose of the study, patients who do not grant informed consent, patients with cognitive impairment whose legal guardians refuse consent to participate, and terminally ill patients.

Data Management

With regard to the sample size, for objectives 1 (incidence) and 1-a (time elapsed until full wound healing) and 1-b (mortality), all immobilized patients registered in SIRUPP will be followed up. To estimate the Braden and MNA predictive values (objective 1-c), we calculated that a sample size of 1700 immobilized patients will be required. Test sensitivity and specificity values of 65% and 70%, respectively, are assumed, together with a PU prevalence of 5%, a statistical confidence level of 95%, and an absolute precision of 10%. For objective 3 (validation of the PU-QoL questionnaire), a sample of 250 patients with PUs will be analyzed (Figure 1). Table 3 presents the variables on sociodemographic and health characteristics.

Figure 1. SIRUPP (Pressure Ulcer Information and Registration System) sample size and study design. PU: pressure ulcer; PU-QoL: Pressure Ulcer Quality of Life; MNA: Mini Nutritional Assessment.



Data Analysis

Data analysis will be performed as follows:

1. To determine PU incidence, the rate will be calculated between the number of new cases of PU over the summed person-years of observation during the follow-up period.
   - To estimate time until wound-healing, survival analysis fitting a Weibull model will be used.
   - To estimate mortality associated with PUs, the mortality rate will be calculated as the number of deaths occurring during the follow-up period over the size of the population participating in the study.
   - To assess the responsiveness to change of the Braden and MNA questionnaires, multiple regression analysis will be used to analyze the relationship between questionnaires' scoring and both incidence of PU and time to wound healing based on the MNA scores. Predictive validity of both questionnaires for detecting the risk of PU development will be measured through the sensitivity, specificity, and positive and negative predictive values as well as the receiver operating characteristic curve.
2. To analyze the HRQoL of immobilized elderly persons with PUs, acceptability, reliability, and validity as compared to the EuroQol 5D-5L questionnaire will be measured
   - To translate, adapt, and validate the PU-QoL questionnaire from English into Spanish, acceptability, reliability, and validity as compared to the EuroQol 5D-5L questionnaire will be measured.
3. To estimate patients' nutritional status (MNA-SF), cognitive status (the Reisberg Global Deterioration Scale), and functional independence (the Barthel scale). Mean values and SDs in all three questionnaires will be calculated.
4. To determine the PU-QoL questionnaire's ability to differentiate between clinical groups (eg, PU severity) and responsiveness to change (eg, wound healing), survival analysis will be performed in order to analyze the relationship between the questionnaire scoring and time to wound healing.

Ethical Considerations

This project has been approved by the Research Ethics Committee in Human Beings, within the Andalusian Public Health System (Granada) under protocol number PI-0086-2016.

Table 3. Database information.

Variable	Description	Coding categories
Sociodemographic variable		
Birthdate	Andalusian Health Service users' database	dd/mm/yyyy
Age	From date of birth until date of database entry	Age in years
Gender	Andalusian Health Service users' database	Female/male
Elderly nursing home	Residence	Unique key
Patient outcomes measures		
Braden scale	Braden score questionnaire (individual subscales and total score)	Discrete numeric value (6-23)
Date of the Braden scale assessment	Date when each repeated Braden questionnaire is completed	dd/mm/yyyy
Identification variables		
NUHSA[a]	Unique identifying electronic health record number within the Andalusian Health Care Service	Unique key
PHCC[b]	Primary health care center where patient is assisted	Unique key
Allocation code	Identifies groups of patients allocated to specific health care teams	Unique key
CNP[c]	Health care practitioners' number	Unique key
Registration date	First database record	dd/mm/yyyy
Follow-up data		
Follow-up status	Patient follow-up or status change	Under follow-up, moved away, deceased
Follow-up status date	Assessment	dd/mm/yyyy
Type of wound	Only pressure ulcers	Pressure ulcers, other wounds of the skin
Date of diagnosis	Date wound was first recorded	dd/mm/yyyy
Date of origin	Date wound was first noticed	dd/mm/yyyy
Wound stage	Stage of pressure ulcer according to GNEAUPP[d]	0: missing, 1-4: stages I-IV, 5: lesions of deep tissues
Wound site	Wound location	46 categories
Associated health care level	Health care level where pressure ulcers appeared	Hospital, nursing home, own home
Date of wound assessment	Next assessment schedule	dd/mm/yyyy
Treatment	As prescribed	Text
Course of treatment	Treatment periodicity	Treatments per time units
RESVECH[e] 2.0	Expected assessment results and chronic wounds healing evolution Score	Discrete scale from 0 (already healed) to 35 (worst possible wound)
Urinary incontinence	Whether incontinence is present at the time of assessment	Yes/no
Barthel scale	Daily living activities index	Discrete scale from 0 (worst state of disability) to 100 (complete autonomy)
GDS[f] scale	GDS	Discrete scale from 1 (no cognitive decline) to 7 (severe dementia)
MNA-SF[g] scale	MNA-SF questionnaire	Discrete scale from 0 (worst nutritional state) to 14 (best nutritional state)
PU-QoL[h] scale	PU-QoL questionnaire (lower scores are indicative of better results)	10 individual discrete numeric subscales: pain (0-16), exudate (0-16), odor (0-12), sleep (0-12), mobility/movement (0-18), daily activities (0-16), vitality (0-10), emotional well-being (0-30), self-consciousness and appearance (0-14), participation (0-18)
Mobility status	Patient mobility assessment	Yes/no

Variable	Description	Coding categories
Date of the mobility status assessment	Initial and subsequent mobility assessment record	dd/mm/yyyy

[a]NUHSA: patient health record number.

[b]PHCC: primary health care center.

[c]CNP: health care practitioners' number.

[d]GNEAUPP: Spanish Advisory Panel on Pressure Ulcers and Chronic Wounds.

[e]RESVECH: wound healing assessment.

[f]GDS: Global Deterioration Scale.

[g]MNA-SF: Mini Nutritional Assessment - Short Form.

[h]PU-QoL: Pressure Ulcer Quality of Life Questionnaire.

Results

The results of this study are currently under analysis. Ethics approval was provided on March 02, 2017. The start meeting with the ZBS coordinators and DSGM management team was celebrated in June 2017. Throughout September and October 2017, 33 ZBSs across the primary health district agreed to participate in the study and received data collection and registration training in SIRUPP database.

As of April 2019, 362 nurses participated in the study by implementing 11,452 Braden tests, 1608 MNA tests, 960 Barthel tests, and 588 GDS tests. A total of 2983 patients consented to participate, of which 2561 were living at home and 422 were living in nursing houses. In addition, 869 patients developed at least 1 PU since the beginning of the project.

The HRQoL questionnaire translation and cross-cultural adaptation started in November 2017. Its forward translation from English into Spanish ended in February 2018 and continued with backward translation until March 2018. The first Spanish version was evaluated by a group of health professionals and patients between April and May 2018, whose recommendation was to develop a second version of the Spanish HRQoL questionnaire. Starting September 2018, a revised Spanish version was developed and is nowadays implemented with a target population for validation purposes.

The data obtained from the SIRUPP study will provide a detailed outlook on the incidence, mortality, and duration of PUs at local and regional levels. To our knowledge, the validated Spanish-language HRQoL instrument will be the first measure of HRQoL specifically developed for Spanish-speaking patients with PUs.

Discussion

The SIRUPP project was proposed in view of the burden that PUs exert on the quality and quantity of the life of elderly people. PUs are largely considered to be a preventable condition. Therefore, the SIRUPP project is focused on the characterization of the epidemiology of PUs in our health care system and social setting, with an emphasis on the incidence of PUs and health outcome variability (time needed for the wounds to heal, mortality rates, and HRQoL).

The following challenges were considered in the design of the SIRUPP study: the potential underrepresentation of immobilized patients in the DSGM due to unreported health cases in the SIRUPP data-gathering system and the possible misclassification of patients as immobilized or the misclassification of the PU stage/category.

HRQoL assessment (corresponding to study objective 3) provides valuable, multidimensional knowledge of this major health care problem from the patients' perspective. The availability of a validated Spanish version of the PU-QoL instrument will be invaluable for optimizing medical decision making for patients with PUs. In addition, this study will allow policymakers to reassess the use and efficacy of evaluation tools currently used in primary health care (ie, the MNA and Braden scales).

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Authors' Contributions

EV conceived the study, which was designed by EV and BG, BG wrote the initial draft and developed successive versions of the manuscript. CD contributed to study design. CR provided critical review of the manuscript and study design of the PU-QoL validation component. MT provided critical appraisal of the first draft and contributed to the structure and content of successive versions of the manuscript. VC contributed to the first draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Progress and Health Foundation (FPS).
[PDF File (Adobe PDF File), 347KB - resprot_v8i8e13701_app1.pdf]

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Abbreviations

DSGM: Granada-Metropolitan Primary Healthcare District
GDS: Global Deterioration Scale
GNEAUPP: Spanish Advisory Panel on Pressure Ulcers and Chronic Wounds
HRQoL: health-related quality of life
PU: pressure ulcer
PU-QoL: Pressure Ulcer Quality of Life
SIRUPP: Pressure Ulcer Information and Registration System
SSPA: Andalusian Public Health System
MNA: Mini Nutritional Assessment
MNA-SF: Mini Nutritional Assessment - Short Form

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Protocol

Exploring Existential Loneliness Among Frail Older People as a Basis for an Intervention: Protocol for the Development Phase of the LONE Study

Anna-Karin Edberg[1], Prof Dr; Ingrid Bolmsjö[2], Prof Dr

[1]The Research Platform for Collaboration for Health, Faculty of Health Sciences, Kristianstad University, Kristianstad, Sweden

[2]Faculty of Health & Society, Malmö University, Malmö, Sweden

Corresponding Author:
Anna-Karin Edberg, Prof Dr
The Research Platform for Collaboration for Health
Faculty of Health Sciences
Kristianstad University
Elmetorpsvägen 15
Kristianstad, SE 291 88
Sweden
Phone: 46 44 250 3975
Email: anna-karin.edberg@hkr.se

Abstract

Background: International research concerning end-of-life issues emphasizes the importance of health care professionals (HCPs) being prepared to deal with existential aspects, like loneliness, in order to provide adequate care. The last phase of life is often related to losses of different kinds, which might trigger feelings of isolation in general and existential loneliness (EL) in particular. There is a large body of research concerning loneliness among older people in general, but little is known about the phenomenon and concept of EL in old age.

Objective: This study aims to describe the framing, design, and first results of the exploratory phase of an intervention study focusing on EL among older people: the LONE study. This stage of the study corresponds to the development phase, according to the Medical Research Council framework for designing complex interventions.

Methods: The LONE study contains both theoretical and empirical studies concerning: (1) identifying the evidence base; (2) identifying and developing theory through individual and focus group interviews with frail older people, significant others, and HCPs; and (3) modeling process and outcomes for the intervention. This project involves sensitive issues that must be carefully reviewed. The topic in itself concerns a sensitive matter and the study group is vulnerable, therefore, an ethical consciousness will be applied throughout the project.

Results: The results so far show that EL means being disconnected from life and implies a feeling of being fundamentally separated from others and the world, whether or not one has family, friends, or other close acquaintances. Although significant others highlighted things such as lack of activities, not participating in a social environment, and giving up on life as aspects of EL, the older people themselves highlighted a sense of meaningless waiting, a longing for a deeper connectedness, and restricted freedom as their origins of EL. The views of HCPs on the origin of EL, the place of care, and their own role differed between contexts.

Conclusions: The studies focusing on identifying the evidence base and developing theory are published. These results will now be used to identify potential intervention components, barriers, and enablers for the implementation of an intervention aimed at supporting HCPs in encountering EL among older people.

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KEYWORDS

study protocol; loneliness; existential; frail older adults; qualitative research; health personnel

Introduction

Background

Research conducted by our group shows that older people receiving municipal care during the last period of life [1], older people in general [2], and severely ill people at the end of their lives [3] all describe the importance of being able to talk to others about existential aspects of life, including their approaching death. Our previous research shows that one of the most significant challenges for health care professionals (HCPs) is communication about existential issues that occur at the end of life [4]. There is, thus, a need for more knowledge about how we can facilitate communication between frail older people and their significant others, and also improve the quality of care. This paper describes the framing, design, and first results of the first exploratory phase of a study focusing on existential loneliness (EL) among older people, the LONE study. This phase corresponds to the development phase, according to the Medical Research Council (MRC) framework [5], and contains both theoretical and empirical studies as a basis for the development of an intervention focusing on supporting HCPs when they encounter EL among older people.

Rationale for the Study

International research concerning end-of-life concerns emphasizes the importance of HCPs being prepared to deal with existential issues in order to provide adequate care and services. One such central existential issue is loneliness. Loneliness is often related to either physical aspects of life, where a need for closeness and touch are in focus, or to social isolation, where a need for human relationships are in focus [6]. Both these aspects can appear at any time throughout life but are more often present when people get older and their social networks shrink. Another aspect of loneliness, described in the literature as EL or existential isolation, can also be experienced throughout life. EL concerns the concepts of meaning and hope [7,8], as well as the awareness of being vulnerable and mortal as a human being [9,10]. During times of grief, worry, and illness, feelings of EL might be enhanced. The last phase of life is often related to losses of different kinds, which might trigger feelings of loneliness in general, and EL in particular. There is a large body of research concerning loneliness among older people in general [11], but little is known about the phenomenon of EL in old age. We, therefore, aim to focus specifically on EL in this project.

What Do We Already Know?

It is not possible to deal with aspects of EL without taking a philosophical point of departure. Existentialists such as Frankl [12], Buber [13], and Sartre [14] have all focused on questions of human existence and the meaning of life. The literature highlights key issues such as freedom, choice, responsibility, and anxiety. The fundamental idea is that we are all, as human beings, free both to choose and to not choose; we alone bear responsibility for all our choices, and as a consequence we face anxiety. In the scientific literature, EL has been looked at from different perspectives, such as philosophy, caring science, social science, gerontology, and psychiatry [7,9,15-18]. Several of these studies confirm that the existential component in loneliness often has an indirect relationship with the concept of meaning [7,8] as well as a search for meaning and hope in the present situation, thereby reducing suffering [19]. When it comes to nursing research, previous research has tended to relate EL to existential suffering, such as a fear of death and being alone [20], instead of considering it as a continuum that can be constructive if it is encountered and validated by others [21]. Other researchers have highlighted that EL is not primarily about suffering but should rather be understood as an awareness of being vulnerable and mortal [9,10]. The concept of EL, thus, has a broad empirical significance, as it is often reinforced when a human being is left on their own in a threatening situation, such as during severe illness [8]. Ettema et al [8] have emphasized that EL is a multifaceted concept that is far from clear, and theoretical as well as empirical research is needed.

EL is often described in relation to dying and death and especially concerning palliative care [22-24]. One of the most difficult challenges for health care staff is caring for people in palliative care at the end of life, as shown by discussions with the patients about their dying and death [24,25]. Similar results have also been reported in studies involving HCPs working in municipal care and services for older people; communicating about dying and death, as well as encountering older peoples' existential needs, was found to be difficult and something that the staff tried to avoid [26]. This, in turn, affected the residents' ability to speak about their existential needs.

HCPs working in palliative care have described how, although they are trained to take care of patients in different crises, they end up experiencing their own unwanted thoughts and feelings about death during that process. This results in a sense of vulnerability, and they thus felt less prepared to handle their patients' existential suffering [27]. Many researchers have pointed out that HCPs must understand their own EL to handle the situation of a patient who is close to death [8,19]. In addition to difficulties in dealing with their own anxiety about death, staff also experienced difficulties in communicating with their patients about EL. Thus, the way the HCPs respond to questions concerning EL is affected by both their own view of dying and their own difficulties in communicating existential issues in encounters with patients or residents and their families.

The next of kin are another group that must be considered when investigating older people's experiences of EL. Although patients may struggle with existential concerns at the end of life, these issues are seldom brought into focus in their care [28] or discussed with their families or close friends. An interview study with 17 participants found that the experience of being next of kin to an older person in the last phase of life was understood as being a devoted companion during the transition toward the inevitable end [29]. This meant that the next of kin were present regardless of whether they were caregivers or not, and that they shared aspects of the old person's everyday life during this final transitionary phase as well as during their last moments. The experience of being next of kin further meant living in the shadow of death, focusing on the needs of the dying person, making adjustments to everyday life, feeling a major responsibility for this person, struggling with the health and social care system, and gaining strength from support [29]. As the next of kin are involved in the care and are emotionally

affected by the situation, their need for support should also be acknowledged.

The way in which HCPs encounter patients' existential issues is clearly related to the context of care. Studies in palliative care have shown that there is a need for research concerning existential issues related to different contexts and cultures of care, as well as the influence of context on the provision of care and service. This knowledge is needed to end patients' sense of isolation and contribute to more health-promoting care [30-32]. We know that specialized and acute care are predominantly characterized by medical life-saving actions [33], while hospice care is characterized by efforts toward a healing environment, and an atmosphere that affirms life and promotes a good death [34]. In special accommodations for older people, there is a strong focus on activities to promote independence [26] even though most people die within the first year after moving in [35]. Thus, the culture and discourse within different care contexts clearly affects the experience of EL among the people being cared for, as well as the HCPs' possibilities to meet with and confirm the experiences of the patients and their next of kin.

There is a lack of any methods for supporting HCPs in identifying and handling EL. Several studies (eg, [24]) emphasize the need for research focusing on how, despite the presence of multiple diseases and severe symptoms, the end of life can be a positive phase of life where hope and joy can coexist with grief and suffering. However, other researchers [8,19] point to the need for clarity concerning both theoretical and empirical evidence on the phenomenon of EL, so that HCPs can better handle it in their daily work and see it from the patients' perspective. If EL is identified and confirmed, both as suffering and a route to inner peace, this might support a feeling of deeper understanding and increased well-being for patients or residents and their significant others, as well as for HCPs.

Aims

We know that caring for people at the end of life is existentially challenging, as dying and death are constantly present, especially in the care of older people. As all frail older people are by definition in the last phase of life, we can assume that they experience EL to some degree. However, EL is a multifaceted phenomenon that needs to be further explored. On the basis of earlier research, we also know that HCPs need support to encounter older people's thoughts about life and death. The aims of the LONE study are thus to:

1. Identify the evidence base for EL, by investigating the aspects and dimensions of EL.
2. Develop a theoretical frame for an intervention by investigating:
    - The meaning of EL from the perspective of frail older people and how EL can be eased.
    - Significant others' experiences of encountering EL, and how they handle situations when their relatives experience EL.
    - HCPs' experiences of encountering older people with EL, the ways in which they identify and handle EL, and their own needs for support.
    - EL in relation to different care contexts.
3. Prepare the modeling process and outcomes for the intervention by:
    - Identifying potential intervention components, as well as barriers and enablers for the implementation of the intervention.
    - Developing an outline for the intervention.

Methods

Overview

This paper describes the exploratory phase of a study focusing on EL among older people, which in turn will form a basis for the development of a complex intervention to support HCPs who care for these people. According to the MRC [5], aspects that determine the complexity of an intervention include the number of components, the number of interactions between components, the number of organizational levels targeted by the intervention, and the number and variability of positive outcomes. The complexity of an intervention is also influenced by how flexible the intervention is. The MRC highlights that the chance of an intervention's success increases if the intervention is adjusted to the actual situation and prerequisites, and also grounded on a solid theoretical, as well as empirical, base [5]. The MRC also points to the fact that different stakeholders need to be involved in the phases of development, testing, and evaluation [36]. In the planning of the LONE study, we were guided by the MRC framework.

According to the MRC [5], there are 4 key elements in the process of developing and evaluating a complex intervention: development, feasibility and piloting, evaluation, and implementation. The first exploratory phase described in this paper corresponds to the development phase, which according to the MRC [5] includes: (1) identifying the evidence base; (2) identifying and developing the theory; and (3) modeling the process and outcomes. We have so far completed the studies relating to identifying the evidence base as well as identifying and developing the theory and are now (in June 2019) about to synthesize the results and model the process and outcomes.

Identifying the Evidence Base

According to the MRC [5], the relevant existing evidence should be identified either through existing systematic reviews or by updating or conducting a new systematic review. As the literature concerning EL is multifaceted, it is very important to describe different aspects and dimensions (constructs) to know what we mean when we talk about EL. Building on an earlier systematic review and concept analysis of EL by Ettema et al [8], we conducted a review of the literature dealing with the concept and phenomenon of EL. The analysis focused on all relevant constructs for our understanding of EL and provided us with a definition, which, in a reciprocal process, has been used as a basis for analyzing the empirical material. This inclusive approach ensured that important perspectives in the studies were not lost.

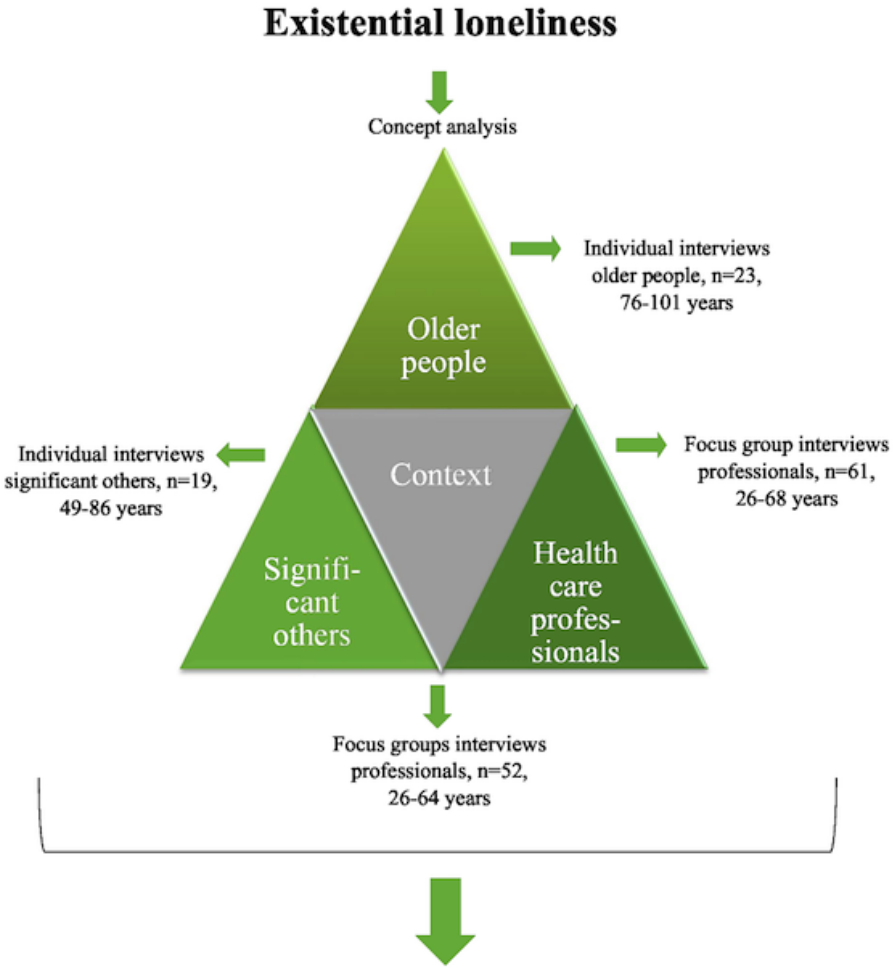
Identifying and Developing the Theory

According to the MRC, it is important to develop a theoretical understanding of the likely process of change by "drawing on

the existing evidence or theory, supplemented if necessary by new primary research, for example interviews with those targeted by the intervention or involved in its development or delivery" [5].

We, therefore, conducted empirical studies focusing on EL among older people through interviews with frail older people, their significant others, and HCPs. For an overview of the different parts, see Figure 1.

Figure 1. Overview of the areas included in the developmental phase of the intervention.



Frail Older Peoples' Experiences of Existential Loneliness and How It Can Be Eased

In total, 23 patients and residents were interviewed concerning their experiences of EL. The criteria for inclusion were: being aged 75 years or older, being able to communicate, and being frail. Even though frailty has become an established concept in research, there is no agreed upon definition [37,38]. One way to operationalize frailty is through a quantitative summary of a number of frailty criteria. For example, Fried et al [39] recommend that 3 or more of the following 5 criteria should be used to identify and measure frailty in clinical practice: weakness, poor endurance, weight loss, low physical activity, and slow gait speed. Another study found that HCPs interpreted the concept somewhat differently, describing qualitative aspects such as being bodily weak and ill, lacking balance in everyday activities, and being dependent in everyday life [40]. As we had limited possibilities to investigate either quantitative or qualitative aspects of frailty when including the participants, we decided to use the somewhat more convenient criterion of being at least 75 years of age, and in need of long-term care or services. We argue that the indicator of long-term care and services fulfils as many as possible of the qualitative and quantitative descriptions of the concept, as in a Swedish context these descriptions are prerequisites for a decision about such support in municipal care [41], or for being registered in home health care or palliative care [42].

We included patients and residents from different contexts: primary care, home care, hospital, special accommodation, and palliative care. In primary care, home care, and special accommodation, the informants were identified by staff. At the hospital, the informants were identified by staff during their stay and invited to participate in connection with their discharge from hospital. In hospices, patients were identified and invited to participate after admission. Due to ethical aspects, people who were obviously in the very final stages of their life and receiving end-of-life care were not included.

The interviews with the patients and residents (n=23) were performed as individual narrative interviews focusing on the experience of EL. A total of 2 interviewers performed the interviews as a pair. The roles of the 2 interviewers were clear before the interview, as one performed the interview while the other sat to one side taking notes, and if needed, picked up clues that were missed during the interview. All interviews were performed by a doctoral student who was supported by a researcher with profound knowledge about interviews with older people and people in palliative care.

The interview started with an introduction to the concepts of loneliness and a deeper sense of loneliness; that is, EL. The informants were then asked for their thoughts about this and whether they could recall any situation when they felt that way. Probing questions were asked concerning the situation, their thoughts and feelings, whether they could or wanted to share their feelings with someone else, and in what way the experience of EL could be eased. At the end of the interview, the patients and residents were asked for permission to invite their next of kin for an interview. They themselves decided which significant other should be asked.

After the interview, the 2 interviewers reflected together on their experience of the interview and what they had learnt about EL during the interview. They also wrote a description concerning the informants' situation and other contextual aspects. The interviews were recorded and transcribed. The first paper was analyzed with a phenomenological hermeneutical analysis [43], as we were interested in the meaning of EL, while the second paper aimed to describe experiences and was analyzed with conventional content analysis [44] using the contextual description as a frame.

The Perspectives of Significant Others

In all, 19 significant others were interviewed concerning their experience of encountering EL among their relatives. The informants were identified by the interviewed patients and residents (as described above), and were spouses, children, siblings, or other persons identified by the older person as being close to them. The interviews were performed as individual narrative interviews, with a focus on narrations about the experience of EL among their relatives. The majority of these interviews were performed by 2 researchers working as a pair, as described earlier. The interview started with an introduction to the concepts of loneliness and EL, and the informants were then asked if they could recall a situation when their relative expressed a feeling of a deeper sense of loneliness or EL. Follow-up questions were asked, such as "How did you notice?," "Do you remember what you thought and felt?," and "How did you handle the situation?". The interviews were recorded, transcribed, and analyzed using conventional qualitative content analysis [44].

Health Care Professionals' Experiences of Encountering Older People With Existential Loneliness, and Their Own Needs for Support

In total, 11 focus group interviews with HCPs were performed. A focus group interview is based on the idea that people develop their views and narrations about their experiences in discussion with others [45]. Each focus group had a median of 6 participants from different professions (registered nurses, physicians, nurse assistants, social workers, occupational therapists, and physiotherapists), totaling 61 professionals. The focus groups were conducted in different care contexts: primary care, home care, prehospital care (ambulance), hospital, special accommodation, and palliative care. Each interview focused on the HCP's experiences of encountering older people expressing EL. The interviews started with an introduction to the concepts of loneliness in general and EL in particular. The participants were then asked if they could recall a situation when, in their interpretation, a patient or resident experienced EL. Follow-up questions were asked, such as "How did you recognize the person's experience?," "How did you handle the situation?," "What did it awake in you?," "How are you prepared to handle such situations?," and "What kind of support do you need?." The interviews were recorded, transcribed, and analyzed using a combination of a deductive and an inductive approach, based on a theoretical framework by van Deurzen [46].

Existential Loneliness in Different Care Contexts

The interviews with HCPs from home care, hospital, special accommodation, and palliative care were analyzed with the material grouped according to context. The characteristics of each context were noted and compared, with a focus on the narratives of the HCPs. The material was analyzed using case study methodology [47].

The Preparation of the Modeling Process and Outcomes

According to the MRC [5], modeling of a complex intervention before a full-scale evaluation can provide important information about the design of both the intervention and the evaluation. This phase will include preparation for this modeling through the identification of potential intervention components, barriers, and enablers for the implementation of the intervention through a qualitative evidence synthesis [48]. The aim of the synthesis will be to identify intervention mechanisms in the data already collected and analyzed in the previously described steps in the LONE study. The synthesis will further aim to identify, among other things, possible barriers and enablers for the intervention related to the context of care, and also search for possible explanations about how the intervention might work in different contexts.

We will also construct a preliminary outline of the intervention aimed at supporting HCPs in encountering EL, using concept mapping [49]. Concept mapping is a group-based method for developing a conceptual framework for an intervention or evaluation. The group participates in recurrent workshops with the aim of generating ideas and assessing their relevance. The results from these discussions are then structured in clusters, and their interrelation is illustrated visually using statistical methods. Different stakeholders (older people, significant others, HCPs, and health care managers) will participate in the concept mapping, and the qualitative evidence synthesis will be used as a basis for discussion and reflection. We have regularly consulted a review panel composed of different stakeholders (HCPs, significant others, and older people) throughout the

study period. They will be especially important during the phase of actually developing the intervention.

Ethical Aspects

This project involves several sensitive issues that need to be carefully reviewed. We are aware that the topic concerns a sensitive matter and that the study group is very vulnerable. We have, therefore, applied an ethical consciousness throughout the project. The voluntary nature of participation by patients, significant others, and HCPs has been emphasized in the information given out about the project and again before the interviews began. All participants gave their written informed consent to participate in the study. A contact person at each involved clinic, health care center, and special accommodation had the main responsibility of making the initial contact with the patients and residents that met the inclusion criteria so as to provide initial information about the project and ask if the researchers could contact them. The researchers then provided oral and written information about the study. After the interview, the contact person was responsible for observing whether the patient or resident had a need for a follow-up discussion. Other staff at the facility did not have any information about which patients or residents were included in the study. Following the interviews with the significant others, one of the interviewers contacted each participant by phone 2 days after the interview to ask whether they had any questions or thoughts that were awakened by the interview. Different pairs of interviewers performed the interviews with the patients or residents and the significant others to ensure that the interview with the significant other was not affected by knowledge about the patient or resident. This also prevented the risk of the significant other receiving information about what the patient or resident had said in their interview, as the researchers interviewing the significant other did not have this information.

Ethics Approval and Consent to Participate

All participants gave their written informed consent to participate in the study. The study has been approved by the Regional Ethical Review Board in Lund, Sweden (ref: 2014-652).

Availability of Data and Material

Due to the sensitive matter of the interviews and the fact that they are in Swedish, raw data will primarily not be made available for researchers outside the research group.

Results

The studies aiming at identifying the evidence base and developing a theoretical frame for an intervention have so far resulted in 7 published papers from 2018 to 2019 and are summarized below.

Identifying the Evidence Base

The concept analysis [50] focused on a clarification of what constitutes EL and describe its lived experiences. The aim was to provide a definition of EL that could function as a tool for identifying the phenomenon and for differentiating it from other kinds of loneliness. The definition that emerged was:

> *EL is the immediate awareness of being fundamentally separated from other people and from the universe, and typically, because of this awareness, experiencing negative feelings, that is, moods and emotions.*

The crucial difference between subjective experience of being socially alone and EL appeared to be that social loneliness is about lacking intimate social relations, whereas EL is concerned with a more basic lack, namely, a feeling of being fundamentally separated from others and the world, whether or not one has a family, friends, or other close acquaintances. Thus, you might have close relations and not suffer from loneliness yet still experience EL [50].

Identifying and Developing the Theory

Frail Older Peoples' Experiences of Existential Loneliness and How It Can Be Eased

The 2 studies focusing on frail older people's experience of EL [51,52] showed that EL mainly means being disconnected from life, that is, being trapped in a frail body, being met with indifference, having no one to share meaningful aspects of life with, and lacking meaning in life [51]. EL can, however, be eased when being acknowledged by others, that is, being the focus of others' concern, encountering intimacy, and having meaningful exchanges of thoughts and feelings. EL could also be eased when bracketing negative thoughts and feelings, that is, when adjusting and accepting the present situation, viewing life in the rear - view mirror, being in contact with spiritual dimensions, and being able to withdraw and distract themselves [52].

The Perspectives of Significant Others

The study focusing on significant others [53] showed that they interpreted that EL emerged when being increasingly limited in body and space, when being in the process of disconnecting, and when being disconnected from the outside world. As the significant others also discussed the reasons behind the experience of EL, we decided to pair and contrast these views with the older persons' narratives [54]. The comparison showed that while significant others highlighted aspects of lack of activities, not participating in a social environment, and giving up on life, the older people themselves highlighted a sense of meaningless waiting, a longing for a deeper connectedness, and restricted freedom as origins of EL [54].

Health Care Professionals' Experiences of Encountering Older People With Existential Loneliness, and Their Own Needs for Support

The study focusing on health care staff's experience of encountering older people with EL [55] showed that HCPs perceived EL to appear in various forms associated with barriers in their encounters. The barriers described were as follows: (1) the older people's bodily limitations (which complicated communication), demands, and needs perceived as insatiable by the staff, which, as a consequence, caused the staff to withdraw; (2) an older person's need for personal privacy that was difficult to get through; or (3) fear and difficulty in encountering existential concerns on the behalf of health care staff [55].

Existential Loneliness in Relation to Different Care Contexts

So far, the impact of context has been analyzed in relation to the narratives from HCPs [56]. The results found differences and similarities among the care contexts concerning the professionals' views on the origins of EL, the place of care, and the professionals' own role. Concerning the origin of EL, the focus in home care and residential care was on life, the present and the past, compared with hospital and palliative care where the professionals mainly related EL to the forthcoming death. The older person's home, as the place of care, was described to help to preserve the older person's identity. In hospital and palliative care, as in institutional care, the place offered security, whereas in residential care, the place could make older people feel like strangers. Creating relationships was considered an important part of the professionals' role in all 4 care contexts, although this had different meanings, purposes, and conditions [56]. This study will be completed with a reanalysis of the interviews with the older persons, sorted by context.

Discussion

Principal Findings

The results from the already published studies will now form the basis for the modeling process and the outcomes of the intervention. So far, we can conclude that an intervention targeting HCPs most certainly needs to be flexible and adjustable to different care contexts and designed as a pragmatic trial [36]. We have also learnt that the experience of EL is individual and that a person-centered approach is necessary. The intervention, thus, needs to include a toolbox of different approaches and methods.

During the progress of the studies performed so far, new areas of interest have emerged, such as contribution from volunteers, the perspective of managers in aged care settings, what kind of support significant others might need, and to what extent coordinators of support to relatives focus on EL in support groups. These studies are at present in progress and will also contribute to the overall design of the intervention program.

Methodological Aspects

All qualitative research should be evaluated in terms of trustworthiness, including credibility, dependability, confirmability, and transferability [57]. One aspect of credibility is accuracy in the selection of informants. In the studies, we strove for a broad variation in experiences by involving older people representing a range of ages, civil statuses, phases of life, and care contexts. This also increases the transferability of the findings. To increase the credibility, we also strove for a variation concerning significant others: spouses, children, and other people close to the patient or resident. Concerning aspects of dependability, the same interview guide was used for all interviews with the same group of informants, and the process of data collection and analysis was closely monitored by the entire research group. The confirmability of the study concerns objectivity, accuracy of the material, relevance, and meaning [57]. In the interview studies, there was a designated group of senior and junior researchers and doctoral students involved in the data collection and analysis of each set of material. The entire research group will be involved in the synthesis of data, thereby enabling a multifaceted analysis while also reducing the impact of individual researchers' preunderstanding of the phenomenon.

Data Management and Quality Assurance

The confidentiality of the participants and the different care facilities involved has been maintained. Documentation of informed consent is kept in a safe, separate from the interview material, and it is thus impossible to link it to the interviews. Original recordings of the interviews are kept on a separate, protected hard drive. The transcripts have been coded, and names, places, and other information that might indicate or reveal the identity of the participants have been omitted. One of the junior researchers was assigned to act as a coordinator to collect and register all informed consent forms from the managers and the patients, and to act as a link between the researchers, the patients and residents, the significant others, and the HCPs. This coordinator was also responsible for storage of the informed consent documentation in a safe. All transcribed material has been organized and is kept in a separate safe. In seeking ethical approval for the study, we stated that the material will not be used for any other purposes and will therefore not be made available to any researchers outside the research group.

The Research Group

The research group includes 5 senior and 3 junior researchers and 3 doctoral students, representing 3 universities in Southern Sweden. The research group also represents several areas, such as nursing, caring sciences, medical ethics, and human geography, thus increasing the possibility to illuminate the phenomenon and concept from different perspectives.

Importance of the Study

The proportion of older people in the population is constantly increasing, and a growing number of older people will thus be the focus of care and services. The quality of care and services for older people is often debated in the media, usually from a perspective of misery. The present research project will contribute to knowledge that can strengthen HCPs and increase the well-being of patients and residents in the last phase of life. The studies are highly relevant from a human perspective in general, as death will inevitably strike us all, and for the situation of the HCPs in particular, as existential issues are one of the largest challenges in nursing care and care of older people. Knowledge and consciousness about different prerequisites for supporting patients, and their significant others', experience of meaning at the end of life depending on the context of care provision also provides us with a basis for the development of an intervention directed toward increasing the ability of the HCPs to counter EL. This, in turn, will have a positive impact on the quality of care.

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Authors' Contributions

A-KE and IB outlined the study, and A-KE had the main responsibility for drafting the protocol. The entire research group reviewed the manuscript, and both authors agreed on the final version.

Conflicts of Interest

None declared.

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Abbreviations

EL: existential loneliness
HCPs: health care professionals
MRC: Medical Research Council

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Protocol

Early Effect Markers and Exposure Determinants of Metalworking Fluids Among Metal Industry Workers: Protocol for a Field Study

Nancy B Hopf[1*], PhD; Eve Bourgkard[2*], PhD; Valérie Demange[2*], MD; Sébastien Hulo[3*], MD, PhD; Jean-Jacques Sauvain[1*], PhD; Ronan Levilly[4], PhD; Fanny Jeandel[5], BSc; Alain Robert[5], PhD; Yves Guichard[5], PhD; Jacques André Pralong[1], MD; Nathalie Chérot-Kornobis[3], MD, PhD; Jean-Louis Edmé[3], PhD; Pascal Wild[1,6], PhD

[1]Department of Occupational and Environmental Health, Center for Primary Care and Public Health (Unisanté), University Lausanne, Lausanne, Switzerland

[2]Department of Epidemiology, National Research and Safety Institute (INRS), Vandoeuvre cedex, France

[3]IMPECS- EA 4483, Department of Occupational Health, Lille University Hospital, Lille, France

[4]Process Engineering Department, National Research and Safety Institute (INRS), Vandoeuvre cedex, France

[5]Toxicology and Biometrology Department, National Research and Safety Institute (INRS), Vandoeuvre cedex, France

[6]National Research and Safety Institute (INRS), Vandoeuvre cedex, France

[*]these authors contributed equally

Corresponding Author:
Pascal Wild, PhD
National Research and Safety Institute (INRS)
Rue du Morvan
CS 60027
Vandoeuvre cedex, 54519
France
Phone: 33 383502194
Email: pascal.wild@inrs.fr

Abstract

Background: Exposure to aerosols from metalworking fluids (MWF) has previously been related to a series of adverse health outcomes (eg, cancer, respiratory diseases). Our present epidemiological study focuses on occupational exposures to MWF and a panel of exposure and effect biomarkers. We hypothesize that these health outcomes are caused by particle exposure that generates oxidative stress, leading to airway inflammation and ultimately to chronic respiratory diseases. We aimed to assess whether MWF exposure, in particular as characterized by its oxidative potential, is associated with biomarkers of oxidative stress and inflammation as well as genotoxic effects.

Objective: The ultimate goal is to develop exposure reduction strategies based on exposure determinants that best predict MWF-related health outcomes. The following relationships will be explored: (1) exposure determinants and measured exposure; (2) occupational exposure and preclinical and clinical effect markers; (3) exposure biomarkers and biomarkers of effect in both exhaled breath condensate and urine; and (4) biomarkers of effect, genotoxic effects and respiratory symptoms.

Methods: At least 90 workers from France and Switzerland (30 controls, 30 exposed to straight MWF and 30 to aqueous MWF) were followed over three consecutive days after a nonexposed period of at least two days. The exposure assessment is based on MWF, metal, aldehyde, and ultrafine particle number concentrations, as well as the intrinsic oxidative potential of aerosols. Furthermore, exposure biomarkers such as metals, metabolites of polycyclic aromatic hydrocarbons and nitrosamine are measured in exhaled breath condensate and urine. Oxidative stress biomarkers (malondialdehyde, 8-isoprostane, 8-hydroxy-2'-deoxyguanosine, nitrates, and nitrites) and exhaled nitric oxide, an airway inflammation marker, are repeatedly measured in exhaled breath condensate and urine. Genotoxic effects are assessed using the buccal micronucleus cytome assay. The statistical analyses will include modelling exposure as a function of exposure determinants, modelling the evolution of the biomarkers of exposure and effect as a function of the measured exposure, and modelling respiratory symptoms and genotoxic effects as a function of the assessed long-term exposure.

Results: Data collection, which occurred from January 2018 until June 2019, included 20 companies. At the date of writing, the study included 100 subjects and 29 nonoccupationally exposed controls.

Conclusions: This study is unique as it comprises human biological samples, questionnaires, and MWF exposure measurement. The biomarkers collected in our study are all noninvasive and are useful in monitoring MWF exposed workers. The aim is to develop preventative strategies based on exposure determinants related to health outcomes.

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KEYWORDS

metalworking fluid; oxidative stress; exposure biomarkers; early effect biomarkers; genotoxic effects; occupational epidemiology

Introduction

Metalworking Fluids and Their Aerosols

Metalworking fluids (MWF) are used to lubricate and cool tools and the workpiece, as well as flush away metal chips during machining, cutting, grinding, and drilling of metals in many manufacturing processes, from small parts in the watch-making industry to large parts in the automotive or steel industries. MWF are classified into two main families [1]: (1) Straight MWF that is mineral oil containing no water; and (2) Aqueous MWF that regroup so-called soluble oils and semisynthetic fluids according to the amount of mineral oils emulsified in water, as well as synthetic fluids that contain no mineral oil. Depending on their type and use, MWF may contain lubricity, antimisting or antiwear additives, corrosion inhibitors and biocides, as well as perfumes or coloring agents.

Other substances potentially present in the aerosols from used MWF are the result of thermal degradation or contamination of the machined metal parts. Thus, MWF may contain: (1) polycyclic aromatic hydrocarbons (PAHs) due to lack of an initial refining stage or due to thermal degradation; (2) nitrosamines, present in aqueous MWF as by-products of the reaction between secondary amines and nitrite; or (3) microorganisms like bacteria or mycobacteria that may be growing in tanks containing aqueous MWF.

The physical process of metalworking generates a complex MWF aerosol consisting of droplets (the oil mist), which may contain solid particles (eg, metals), and a vapor phase (air or organic vapors). This vapor phase is the result of the evaporation of volatile or semivolatile constituents from the MWF in contact with the hot cutting zone. These aerosols can reach the workers' breathing zone and may remain in suspension for several hours [1]. The size distribution of the MWF aerosols is highly variable (median aerodynamic diameters ranging from 1.8-17 μm) and may contain ultrafine particles (aerodynamic diameter <0.1μm) [2]. MWF aerosols may be inhaled or enter the body through skin contact. Exposure from soiled clothing and ingestion (hand to mouth contamination) are also possible. Consequently, assessing occupational exposure to MWF aerosols has many challenges.

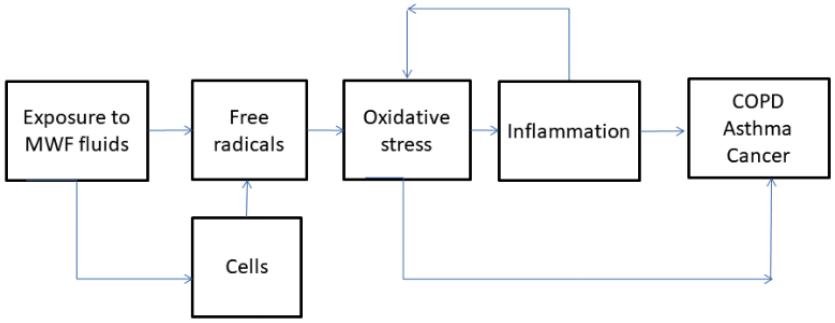
Health Effects From Exposure to Metalworking Fluids

Historically, exposure to poorly refined straight oil-mists has been related to cancer of the skin and the scrotum [3]. More recently, there is growing evidence of a relationship between exposure to straight MWF and bladder cancer [4,5]. As early as the 1990s, exposure to oil-mist was related to acute bronchial hyperresponsiveness, occupational asthma, hypersensitivity pneumonitis, ventilatory impairments and respiratory symptoms [6-9]. Recently, a causal model was applied [10] to explore the quantitative relationship between exposure to MWF aerosol and chronic obstructive pulmonary disease (COPD).

Presumed Physiopathological Mechanisms

Inflammation is hypothesized to be an important process that explains some of the observed health outcomes. Indeed, in vivo chronic exposure to rather high concentrations of different semisynthetic MWF have resulted in inflammation in rat and mice lungs [11]. In addition, signs of oxidative stress have also been reported on the skin of vitamin E deficient mice exposed to MWF [12]. Based on this, Figure 1 (adapted from Ayres et al [13] who presented this mechanism for environmental particulate exposure) summarizes the presumed physiopathological mechanism. Given the multiplicity of health outcomes that have been related to oil-mist exposure, we assumed that the main, common mechanism of these effects was oxidative stress. Briefly, the exposure to the MWF aerosols generates free radicals in the lungs of both exogenous and endogenous origin and thereby causes oxidative stress. This oxidative stress induces inflammation, which ultimately increases the oxidative stress via a feedback mechanism. Thus, this chronic inflammation eventually leads to chronic adverse health effects.

Figure 1. Presumed physio-pathological mechanism adapted from Ayres et al. (2008).



Methods

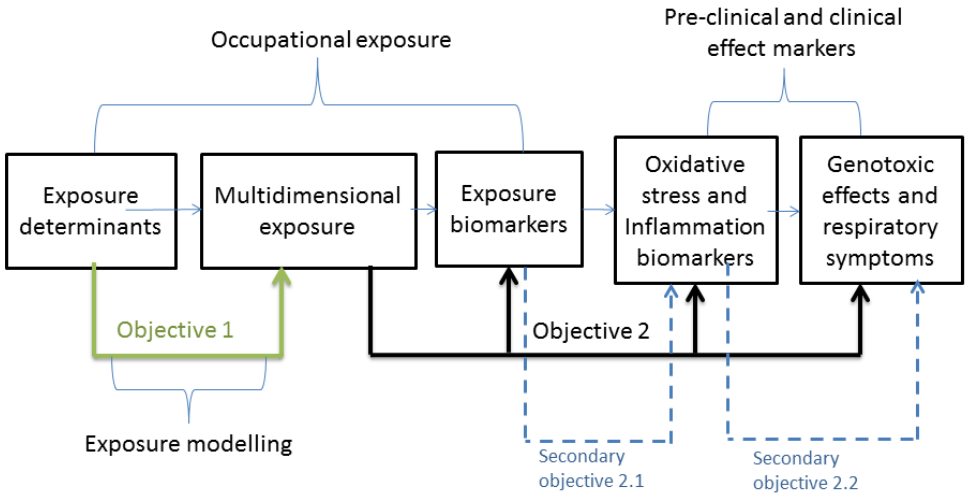
The Study Protocol

The Study Objectives

The study protocol very closely followed the mechanistic pathway outlined in Figure 1 by proposing an epidemiological field study in both the Swiss micromechanical industry and the French metal industry. It assessed the exposure to MWF approximating the biological effect dose, the oxidative stress, inflammation, genotoxic cellular modifications, and the early nonspecific effect biomarkers that might be on the pathways that lead to chronic respiratory diseases.

The ultimate objective is to develop exposure reduction strategies based on exposure determinants that best predict MWF-related health outcomes. This ultimate objective is broken down into several partial objectives summarized in Figure 2. The first primary objective of the study, though, was to establish relationships between the exposure determinants and the exposure measurements. The second primary objective was to establish relationships between occupational exposure, especially oxidative potential, and preclinical and clinical effect markers. There were also two secondary objectives, which included establishing relationships between exposure biomarkers and biomarkers of effect in exhaled breath condensate (EBC) and Urine, as well as establishing relationships between biomarkers of effect, genotoxic effects and respiratory symptoms.

Figure 2. Schematic presentation of the study objectives.



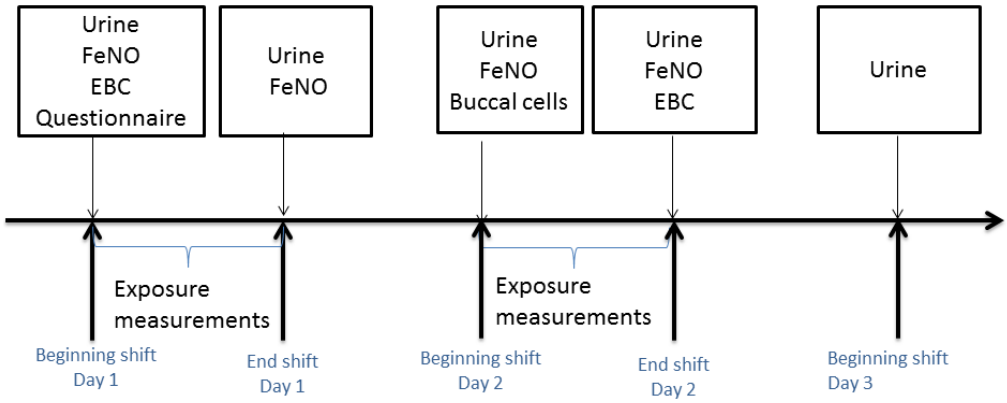
Protocol of the Epidemiological Field Study

A three day long longitudinal study of exposed versus nonexposed workers, after a nonexposed period of at least two days, was conducted in Swiss and French companies. At least 30 workers were exposed to straight oil and 30 workers were exposed to water-based MWF. Nonexposed workers from the participating companies will be included, at a ratio of 2 exposed for 1 nonexposed.

The exclusion criteria for this study were: (1) known chronic or acute respiratory diseases; and (2) known exposure to particulate substances with a potential effect on oxidative stress.

The data collection is summarized in Figure 3. It will consist of repeated characterization of airborne exposure during two consecutive days and multiple collections of EBC, urine and fractional exhaled nitric oxide (FeNO) in parallel. Buccal cells will be collected once per participant. A questionnaire that explores respiratory symptoms, sociodemographic factors (smoking and clinical history, age, etc), the present job, tasks, personal protective equipment, and the participant's job history will also be applied.

Figure 3. Schematic presentation of the field study protocol. EBC: exhaled breath condensate; FeNO: fractional exhaled nitric oxide.



EBC will be collected at the beginning of the shift on Day 1 and at the end of Day 2. Urine samples will be collected at the beginning of shift on Days 1, 2 and 3 as well as at the end of the shift on Days 1 and 2. The FeNO will be measured at the beginning and end of shift on Days 1 and 2. The exposure measurements will be obtained over the shifts of Day 1 and 2. In addition to these data, the occupational hygienists will record workers' tasks and the corresponding exposure determinants. Finally, samples of both used and new MWF will be obtained.

Exposure and Health Outcome Assessment

Table 1 summarizes the different outcomes measured during the field study.

Table 1. Outcomes measured in the field study.

Outcome type	Measured outcome	Method
Exposure determinants	Determinants	Questionnaire
Exposure measurements		
Personal sampling	• Standard gravimetric exposure • Organic carbon • Measurement of ultrafine particle numbers	• Metropol M-282 • Thermal degradation method • Real time instrument
Stationary sampling	• Standard gravimetric exposure • Oxidative potential • Aldehydes • Metals • Organic carbon • NO_2^-[a], NO_3^-[b] • Measurements of ultrafine particle numbers	• Metropol M-282 • Ferrous oxidation-xylenol orange method • Metropol M4 and M66 • Metropol M122 • Thermal degradation method • Ion chromatography • Real time instrument
Monitoring of new and used MWF[c]	• Oxidative potential • Metals • Organic carbon • Benzo(a)Pyrene	• Ferrous oxidation-xylenol orange assay • ICP-AES[d] • Thermal degradation method • HPLC-Fluo[e]
Biomarkers of exposure		
In exhaled breath condensate	• NO_2^-/NO_3^- • Metals	• Ion chromatography • ICP-MS[f]
In urine	• NDELA[g] • 1-OHP[i], 3-OHBaP[j] (PAH[k] metabolites) • Metals	• HPLC-MS/MS[h] • HPLC-Fluo • ICP-MS
Biomarkers of effect		
In exhaled breath condensate	• MDA[l], 8-isoprostane (markers of lipid peroxidation) • 8-OHdG[m] (marker of DNA oxidation) • Formate, NO_2^-/NO_3^- (proposed markers of nitrosative stress)	• HPLC-MS/MS • HPLC-MS/MS • Ion chromatography
In urine	• MDA, 8-isoprostane (markers of lipid peroxidation) • 8-OHdG (marker of DNA oxidation)	• HPLC-MS/MS • HPLC-MS/MS
Other effect markers	• Micronuclei in buccal cells (marker of genotoxicity) • Fractional Exhaled Nitric Oxide (marker of eosinophilic inflammation) • Respiratory symptoms	• Buccal micronucleus cytome assay • Direct-reading instrument • Standardized questionnaire

[a]NO_2^-: nitrite

[b]NO_3^-: nitrate

[c]MWF: metalworking fluids

[d]ICP-AES: inductively coupled plasma atomic emission spectroscopy

[e]HPLC-Fluo: high-performance liquid chromatography with fluorescence detection

[f]ICP-MS: inductively coupled plasma mass spectrometer

[g]NDELA: N-nitrosodiethanolamine

[h]HPLC-MS/MS: high-performance liquid chromatography coupled to tandem mass spectrometry

[i]1-OHP: 1-hydroxypyrene

[j]3-OHBaP: 3-hydroxybenzo(a)pyrene

[k]PAH: polycyclic aromatic hydrocarbons

[l]MDA: malondialdehyde

[m]8-OHdG: 8-Oxo-2'-deoxyguanosine

Exposure Determinants

Exposure determinants are factors within the workplace that contribute to increasing or reducing exposure concentrations [14]. A questionnaire has been developed based on the literature [1,15] and will be used by the occupational hygienists during the field study.

Multidimensional Features of Exposure

Respirable Aerosol Exposure

The respirable particulate MWF mass fraction from personal and stationary sampling will be determined following a reference gravimetric method (INRS Metropol M-282). As a complement to these measurements, the organic carbon content of the aerosol collected on quartz filters will be determined using a specifically modified thermal degradation method [16]. The MWF concentration of the volatile organic fraction will be sampled using a sorbent tube and analyzed chemically. The combination of these measurements will be used to evaluate the overall airborne MWF.

Oxidative Potential

Using the particulate oxidative potential as an additional metric for evaluating possible toxic effects is a relatively new concept and has rarely been used in occupational health studies. In our study, the oxidative potential of the MWF themselves (new and used) for the respirable fraction of the aerosol, as well as for the gaseous phase, will be quantified. The oxidative potential method used will be based on the ferrous oxidation-xylenol orange method [17]. Briefly, MWF was sampled with a teflon filter for the particulate phase followed by a XAD-2 sorbent tube for the gaseous phase. An acidic solution of iron(II) (Fe^{2+}) with xylenol orange as the indicator and sorbitol as a catalyst (ferrous ion oxidation [FOX] solution) was prepared. Oxidation of Fe^{2+} to iron(III) (Fe^{3+}) was followed by calorimetry using a spectrometer. Increasing hydrogen peroxide (H_2O_2) (aq) (0-10 uM) concentrations were used for calibration for the filters and in dimethyl sulfoxide for the XAD-2 sorbent. The teflon filter with the particulate MWF was punched and dropped into the FOX solution, vortexed (1 min), and analyzed. The XAD-2 sorbent was desorbed with dichloromethane, evaporated, resuspended in dimethyl sulfoxide, and analyzed.

Components in the Metalworking Fluid Aerosol

The metal content (eg, iron (Fe), copper (Cu), aluminum (Al), zinc (Zn), manganese (Mn), antimony (Sb), cobalt (Co), nickel (Ni), chromium (Cr), molybdenum (Mo), vanadium (V) and titanium (Ti)) of the aerosol will be measured using stationary samples with cellulose acetate filters, which will be mineralized and analyzed using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Finally, aldehyde concentrations including acetaldehyde and formaldehyde will be quantified.

Real Time Measurement of Ultrafine Particles

Exposure to ultrafine particles might be related to adverse health effects, and ultrafine particles are present in MWF aerosol [2]. Particle number concentration of ultrafine particles will be measured using a real time particle counter (DiscMini) in the 10-500 nm range. The particle size distribution between 0.25-32 µm will be determined with an optical particle counter (Grimm Optical Particle Counter 1.109, 31 channels).

Exposure Biomarkers

EBC is an emerging technique that is simple, noninvasive and allows scientists to study processes in the lungs [18]. The metal concentrations in EBC (eg, Fe, Mn, Cr, Ni, Cu, Zn) will be determined with an inductively coupled plasma mass spectrometer (ICP-MS) using the analytical Totalquant technique with external calibration [19,20].

We will measure the following urinary exposure biomarkers: metals (27 metals), a nitrosamine (N-nitrosodiethanolamine [NDELA]) and two PAH metabolites (1-hydroxypyrene [1-OHP], a metabolite of pyrene, and 3-hydroxybenzo(a)pyrene [3-OHBaP], a metabolite of benzo(a)pyrene). Metals will be analyzed using ICP-MS [21], whereas the PAH metabolites will be analyzed using high-performance liquid chromatography with fluorescence detection (HPLC-Fluo) [22]. Finally, a more sensitive method for analyzing urinary NDELA will be developed based on high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS).

Inflammation and Oxidative or Nitrosative Stress Biomarkers

Inflammation Biomarker

Nitric oxide is a biomarker of bronchial inflammation often used [23] in an occupational context, and it is related to other inflammation markers like nonspecific bronchial hyperresponsiveness, a presumed precursor of asthma [24]. FeNO is a noninvasive and easy method of measuring nitric oxide, with standardized commercial devices (Niox Vero) available.

Oxidative or Nitrosative Stress Biomarkers in Exhaled Breath Condensate

Following Basu [25]:

> *Isoprostanes, mainly 8-iso-PGF2αand 8-iso-PGE2, possess potent biologic effects in a number of biologic systems, and thus they may also serve as pathologic mediators of oxidant stress through their vasoconstrictive and inflammatory properties.*

8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) is a marker of a pathway in the free radical lipid peroxidation mechanism, and therefore fits our presumed mechanism shown in Figure 1. Malondialdehyde (MDA) is another indirect marker of lipid peroxidation, although it is considered less specific. Concentrations of 8-Oxo-2'-deoxyguanosine (8-OHdG) are considered a trace of a repairing/excretion mechanism for oxidized guanine and are considered a measure of whole-body oxidative stress. 8-isoprostane and 8-OHdG will be analyzed following the publication by Syslova [26] using HPLC-MS/MS. The same technique will be used for MDA analysis after a derivatization step.

Nitrites and nitrates have previously been identified as pollutants in aqueous MWF and are markers of nitrosative stress [27,28]. These two anions will be measured in EBC by ion chromatography.

Oxidative Stress Biomarkers in Urine

8-isoprostane, MDA and 8-OHdG will also be analyzed in the urine using HPLC-MS/MS [29,30].

Genotoxic Effects and Respiratory Symptoms

Markers of Genotoxicity

Genotoxicity from MWF aerosol exposure will be assessed using the buccal micronucleus cytome assay [31]. The presence of micronuclei in buccal cells is considered a sign of damage to the DNA and of chromosomal instability. Buccal cells will be harvested from each participant. Using a microscope with white and fluorescent light, the cells will be stained using cytoplasmic and DNA staining and then 2000 cells will be scored for the presence of micronuclei or nuclear buds. A number of occupational exposures have given rise to excess numbers of micronuclei [32].

Respiratory Symptoms

Symptoms of chronic bronchitis and asthma-like conditions will be explored using the standardized Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) questionnaire [33]. In addition, the questionnaire will ask for cutaneous symptoms (eczema or eczema-like symptoms).

Statistical Methods and Power

The statistical analysis will follow the presumed causal model (Figure 2) and will be performed using the Stata (StataCorp LP, College station, Texas) statistical software. The first analysis will model the exposure measurements as a function of the determinants using linear models, after suitable transformations (logarithmic) if necessary. The exposure biomarkers in EBC and urine will be modelled as a function of the exposure measurements as well as possibly the exposure determinants. These analyses will focus on the within-shift evolution of these markers and will be based on mixed models. Measurements below the limits of detection will be included using specific models (random effect Tobit or Bayesian models) [34]. The biomarkers of effect and the FeNO will be analyzed as a function of the exposure measurements and determinants using similar statistical models. Again, the focus will be on the within-shift evolution but also on the evolution over the three days. The effects from the circadian cycle will be controlled by the simultaneous modelling of the nonexposed subjects. The prevalence of symptoms and the frequency of micronuclei will be analyzed using logistic regression as a function of the exposed or nonexposed status and the chronic occupational exposure that will be estimated from the job history and the exposure determinants. Note that in the analysis of the frequency of micronuclei, the number of collected cells per subject will be included as an offset and that this analysis will account for a possible overdispersion using a negative binomial regression. Possible confounders such as smoking, age, sex and diet will be accounted for in the different statistical analyses.

The study size was determined based on the longitudinal evolution of FeNO and the comparison of the frequency of micronuclei in two exposure groups. According to Bohadana et al [35], a 10% increase of FeNO between 2 measurements corresponds to an 80% power at a 5% significance level with a sample of 30 subjects.

With respect to micronuclei, assuming a 0.74% [36] baseline prevalence among controls, we have an 80% power at a 5% significance level with two samples of 30 subjects. This allows us to detect a 2.2 rate ratio between an exposed and a nonexposed group assuming a 1.5 between-subject geometric SD.

The rationale behind choosing the number of controls in a 1:2 ratio to exposed workers is to get equal sized exposure groups between the aqueous exposed works, the straight oil exposed workers, and the controls.

Study Organization

The present study is carried out by a consortium of three organizations: (1) Team 1, the research team EA 4483 from the IMPact de l'Environnement Chimique sur la Santé humaine (IMPECS; Impact of the chemical environment on human health) of the University of Lille in France; (2) Team 2, Unisanté, the department of occupational and environmental health from the University of Lausanne in Switzerland; and finally (3) Team 3, the Institut National de Recherche et de Sécurité (INRS; French National Institute for Research and Safety) in France.

The study is coordinated by the INRS. A Consortium Agreement specifying the legal, financial and scientific framework of the cooperation regarding the present study was signed by the three organizations on March 22, 2017.

Two parallel groups of scientists in Switzerland and France with common operational procedures carry out the on-site data collection. To minimize laboratory bias, most of the samples are dispatched to and analyzed by one laboratory only. All organic biomarkers in urine and EBC, as well as the micronuclei frequency in buccal cells, will be analyzed by team 3. The metals in EBC will be analyzed [14] by team 1. Team 2 will characterize MWF aerosol for its oxidative potential, organic carbon, nitrate, nitrite and aldehyde content as well as the formate concentration in EBC. Both Team 2 and 3 will determine the particulate exposure.

All electronic documents related to the study are deposited in a structured, encrypted extranet located on a server of team 3. The access to this extranet is strictly restricted to the study team members by an individual password. Measurement data from each lab will be deposited by the laboratories generating them. All deposited data will be anonymous, and the rules for generating the identification codes are defined by an operational procedure. The data on the extranet will be saved daily and backups will be kept in a separate building from the server. The deposited data will be organized and prepared for data analysis in the three months after collection by the same data manager, who will provide regular feedback on the data collection.

Ethics and Data Dissemination

This study was approved by the ethical committee of the canton Vaud, Switzerland (Commission cantonale d'éthique de la recherche sur l'être humain CER-VD) on June 13, 2017, project number 2017-00630, and by France (Comité de Protection des

Personnes Sud-Est) on May 17, 2017, project number 17-02-EE-VD/OXIGENOCOM.

Several scientific, peer-reviewed publications are planned. The first ones will correspond to the preparatory phases (eg, a scientific article on the determination of biomarkers in EBC, a paper on automatic versus human-based counting of micronuclei in buccal cells). The other planned papers will respectively correspond to the objectives described in the beginning of this paper.

The ultimate objective is to develop relevant exposure reduction strategies. The results will be published in a nonscientific format and will be accessible by environmental health and safety professionals.

Depending on the corresponding legal authorizations, parts or all of the data will be deposited on a public data repository after the final publications.

Results

Our study is organized into three partially overlapping periods. The first period started October 2016 and ended December 2017 and was dedicated to: (1) obtaining the ethics committees' consents; (2) writing and agreeing on operational procedures; (3) setting up a study-specific data extranet; and (4) validating analytical laboratory procedures.

The second period started with a pilot study conducted from February 12, 2018 to Feb 14, 2018. The subsequent debriefing led to minor adjustments of the daily organization of the data collection. The data collection will end in June 2019. At the time of writing, 100 subjects from 17 companies have been included, comprising 29 control subjects. An additional three companies will be included.

The third period consists of laboratory analysis, data management, and data analysis. Written feedback will be provided to participants and companies related to exposure. Finally, a scientific report will be sent to the funding agency in April 2020, and results will be published in peer-reviewed journals.

Discussion

A strength of this project is its hypothesis driven and multidisciplinary approach. First, the diversity of biomarkers will shed some light on the physiopathological mechanisms. Second, the extensive exposure assessment by occupational hygienists will help in characterizing components that have a short-term effect on the measured biomarkers. Finally, recording exposure determinants will help with focusing the future exposure preventions so that they have the greatest potential impact on workers' health.

One of the most interesting parameters is the oxidative potential of the MWF aerosol. We hypothesize that oxidative potential is a measure capturing the overall oxidative stress generated by the aerosol and would thus be independent of the inert (or nonreactive) constituents such as hydrocarbons. Thus, one of the most interesting relationships to be explored is between oxidative potential and the biomarkers of effect, in particular the biomarkers of oxidative stress. In the words of Dr Ken Donaldson [13]:

> *The measurement of the oxidative potential of ambient particles would represent a more refined metric, bringing it closer to the Biological Effect Dose with anticipated improvements in risk management and better associations with adverse health effects in epidemiological studies.*

Indeed, diverse approaches to assessing occupational exposure give us the tools to characterize what might be the biological effect dose.

Another strength is the noninvasive biomarker collection approach. Respiratory symptoms and urinary biomarkers, and to a lesser extent FeNO, are often used in occupational epidemiology. EBC and micronuclei frequencies in buccal cells are not routinely used yet; however, these biomarkers have shown great promise in earlier work from our research group [28,29,32,37,38]. Thus, the markers developed in this project could potentially be used in routine monitoring of exposed workers.

An important aspect of our study is that the relationships we want to study are in two different time-frames. The relationships between the exposure measurements and the evolution of the biomarkers, be they measured in exhaled air, its condensate or in urine, reflect short-term relationships. The second time frame we consider is chronic. Neither the respiratory symptoms nor the micronuclei frequency are assumed to vary in the 2 days of data collection. These outcomes are therefore obtained only once and reflect long-term effects. To some extent, we could also consider the effect markers measured Monday morning as possible long-term markers. However, when analyzing these outcomes as a function of exposure, we have to consider long-term exposure. The latter is necessarily less precise than the measured exposure because it has to be assessed using the jobs' histories and tasks recorded in the questionnaire.

The constraints of our study protocol entailed a very intensive field data collection from no more than 4 study subjects, with 4 researchers and technicians present in the companies over 4 days. This is the drawback of the very complete exposure assessment, but also of the required participation time from each worker, and finally of the required 2-day unexposed period before inclusion. The total sample size is thus limited. To be able to identify the exposure measurements that are closest to the biological effective dose, it will be necessary to include workers, and hence companies, with varied exposure characteristics both qualitatively and in terms of exposure concentrations. Bacterial contamination and endotoxin measurements were not included due to limited resources. Nevertheless, our protocol reflects a multidisciplinary approach and allows small or very small companies to be included. Consequently, the likelihood of having high exposure levels is greater compared to large companies, which are the ones usually explored in epidemiological studies.

Thus, the possible lack of power induced by the relatively small number of included subjects will be compensated for by the

large exposure variance when including both highly exposed and less exposed workers. It is noteworthy that the repeated measure design (five measurements per subject for urine and two for EBC) will contribute to increase the power of detecting short-term effects.

For outcomes collected only once reflecting long-term effects (respiratory symptoms or micronuclei), the power will correspondingly be lower, especially as the chronic exposure estimate will be less precise and possibly affected by exposure misclassification. As shown previously, one would need an odds ratio greater than 2 to be able to detect such effects.

Related to statistical power is the issue of multiplicity. Indeed, the number of outcomes will be quite large, so a number of statistical models will be fitted to more or less the same data. Thus, with the exception of the central hypothesis relating oxidative potential measurements to oxidative stress, it will certainly be safe to consider some analyses as exploratory or to assign some multiplicity correction to any *P* value.

Conclusion

This study is unique, as it comprises human biological samples, questionnaires, and MWF exposure measurement. The aim is to develop preventative strategies based on exposure determinants related to health outcomes. To achieve this goal, this integrative multidisciplinary approach quantifies the relationships between exposure determinants, exposure measurements, biomarkers of exposure, biomarkers of effect, and early effect outcomes.

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Authors' Contributions

JJS, NBH, RL, SH, EB, VD and PW jointly developed the protocol, with their respective specialties in chemistry, industrial hygiene, occupational medicine, epidemiology and statistics. YG provided insight into toxicology, FJ and AR into biomonitoring and NCK, JP and JLE into biochemistry and occupational health. The project is coordinated by PW, who wrote the first draft of this paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

1-OHP: 1-hydroxypyrene
8-iso-PGE2: 8-isoprostaglandin E2
8-iso-PGF2α: 8-iso-prostaglandin F2α
8-OHdG: 8-Oxo-2'-deoxyguanosine
Al: aluminum
Co: cobalt
COPD: chronic obstructive pulmonary disease
Cr: chromium
Cu: copper
EBC: exhaled breath condensate
EGEA: epidemiological study on the genetics and environment of Asthma, bronchial hyperresponsiveness and atopy
Fe: iron
Fe2+: iron(II)
Fe3+: iron(III)
FeNO: fractional exhaled nitric oxide
FOX: ferrous ion oxidation
H2O2: hydrogen peroxide
ICP-AES: inductively coupled plasma atomic emission spectroscopy
ICP-MS: inductively coupled plasma mass spectrometer
IMPECS: IMPact de l'Environnement Chimique sur la Santé humaine
INRS: institut national de recherche et de sécurité
MDA: malondialdehyde
Mn: manganese
Mo: molybdenum
MWF: metalworking fluids
NDELA: N-nitrosodiethanolamine
Ni: nickel
PAH: polycyclic aromatic hydrocarbons
Sb: antimony
Ti: titanium
V: vanadium
Zn: zinc

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Protocol

Family Members' Perspectives of Health Care System Interactions With Suicidal Patients and Responses to Suicides: Protocol for a Qualitative Research Study

Erin Bryksa[1*], BSW; Reham Shalaby[2*], MD; Laura Friesen[1*], MEd; Kirsten Klingle[3*], MEd; Graham Gaine[1*], PhD; Liana Urichuk[1*], PhD; Shireen Surood[1*], PhD; Vincent Agyapong[2*], MD, PhD

[1]Addiction and Mental Health, Alberta Health Services, Edmonton, AB, Canada

[2]Department of Psychiatry, University of Alberta, Edmonton, AB, Canada

[3]Department of Educational Psychology, Faculty of Education, University of Alberta, Edmonton, AB, Canada

[*]all authors contributed equally

Corresponding Author:
Vincent Agyapong, MD, PhD
Department of Psychiatry
University of Alberta
1E1 Walter Mackenzie Health Sciences Centre
8440 112 St NW
Edmonton, AB, T6G 2B7
Canada
Phone: 1 (780) 407 6504
Email: agyapong@ualberta.ca

Abstract

Background: Suicide is a major cause of preventable death globally and a leading cause of death by injury in Canada. To support people who experience suicidal thoughts and behaviors and ultimately prevent people from dying by suicide, it is important to understand the individual and familial experiences with the health care system.

Objective: This study aims to explore how suicide victims, and their family members, interacted with the health care system.

Methods: We will invite family members of 6 to 8 suicide victims to participate in the study by sharing their perspectives on both their relative's as well as their own interactions with the health care system. Interviews will take place in-person and will be audio recorded, transcribed, and analyzed thematically.

Results: The results of the study are expected to be available in 12 months. We expect the results to shed light on the experiences of suicide victims and their family members with the health care system.

Conclusions: Our study results may inform practice, policy, and further research. They may shape how members of the health care system respond to people who are at risk of suicide and their families.

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KEYWORDS

suicide; family members; public health systems research

Introduction

Background

Suicide is a serious global public health problem, with an estimated 800,000 people reported to have died by suicide every year [1]. In Canada, suicide remains the 9th leading cause of death and the 2nd leading cause of death among children, the youth, and young adults [2]. There were a total of 3978 suicides in Canada in 2016 [3], with more than 500 of these deaths occurring in Alberta. This is more than the number of deaths that occurred that year because of motor vehicle collisions [4]. Health care systems play a vital role in suicide prevention. A study in Alberta, for instance, found that the majority of people who died by suicide used a health care service in the year before their death. They were also more likely to use the emergency

departments, in-patient services, or community mental health services than those who died from other causes, and typically, they used health care services for mental disorders [5].

In Edmonton, which is the site of this study, suicide prevention initiatives are underway to enhance aspects of the health care system, as evidenced by the Implementation Plan for the Edmonton Suicide Prevention Strategy [6]. Yet, beyond stakeholder engagement [7] and an understanding of the dimensions of service quality [8], little is known locally about how individuals who die by suicide and those close to them experience the health care system. The current mechanism by which the Alberta Health Services (AHS) investigates suicide is through the Quality Assurance Review (QAR). The QAR aims to "assess and evaluate the provision of health care service from a system perspective with the goal of improving the quality of services provided" [9]. Although QARs are done following a suicide, on a case-by-case basis, the results are not shared beyond those directly involved. The privacy of the QAR limits case comparison and knowledge translation. In addition, an understanding of the context of death by suicide is needed, as it is thought to differ from the context of a suicide attempt. In 1 study, although the groups were generally the same on measure of depression, completers were significantly more likely to have experienced significant job stress and financial problems, left a suicide note, and used alcohol and drugs before the act [10]. The AHS is committed to patient- and family-centered care [11], which highlights the importance of talking to families about their own and their relatives' experiences with the health care system. Ultimately, insight into the experiences of people who die by suicide and their family members has the potential to inform policy and practice in shaping how members of the health care system, and the AHS specifically, respond to individuals who are at risk of suicide.

Objective and Research Questions

The purpose of this study was to better understand how suicide victims and their family members interacted with the health care system. Our specific research questions include the following: (1) How do individuals impacted by the suicide of a family member perceive their relative's interactions with the health care system? (2) How do individuals impacted by the suicide of a family member perceive their own interactions with the health care system?

Conceptual Framework

The conceptual framework is based on empirical evidence, suggesting that it is not only individual and family and societal factors that contribute to deaths by suicide but also factors related to health care systems (as shown in Textbox 1 [1,12-35]). The framework has been developed through a general review in the literature aimed at providing an evidence-based material supporting all possible risk factors for suicide. Although focusing on health care system risk factors alone would clearly support our hypothesis, we opted to conceptualize the study based on all possible risk factors, including family and social factors such as stigma, social status or public education [1,12], as well as individual factors such as gender, prior history of attempted suicide or psychiatric illness [1,13-15], which we expect to be identified by our participants throughout the data collection. This work would subsequently help in providing a framework for formulating a supplementary quantitative study, which would use descriptive and inferential statistical analysis to explore risk factors for suicide in a provincial or national sample of family members who have been impacted by the death of a loved one through suicide.

Findings from the study will illuminate strengths of the health care system and aspects of care in need of further improvement and refinement. The recommendations arising from this study have the potential to lead to significant system enhancements and reduce suicide rates in Alberta and beyond.

Textbox 1. Conceptual framework of factors contributing to deaths by suicide. The conceptual framework was developed by the authors based on existing literature.

Health systems factors

- Staff attitude toward suicidal persons [12]
- Recency of hospitalization for attempt suicide and recent health care contact [12,13,16,21,30]
- Underdiagnoses of mental disorders and major depressions [31]
- Brevity of interaction with the medical staff [32]
- Ignoring the warning signs of suicide by the health care providers [33]
- Lack of trust in the health care services [34]
- Relatives feeling of exclusion from treatment information [33]

Family/societal factors

- Higher versus low- and middle-income countries [1]
- Stigma and taboo [1]
- Public education [12]
- Interpersonal problems [19]
- Family positive/negative life events and social support [22,23]
- Family history of suicide [24,27]
- Familial difficulty in seeking help outside the social network [35]

Individual factors

- Prior history of attempted suicide [1]
- Psychiatric illness [13-15]
- Gender [1,17]
- Race/Ethnicity [17]
- Age [17]
- Relationship problems/losses [18]
- Recent/impending crisis [18]
- Education level [19]
- Alcohol/substance abuse [19,28,29]
- Marital status [20]
- Hopelessness [25]
- Vulnerable groups with discrimination experience [1,26]

Methods

Study Design

This study uses qualitative research design with key informant interviews where sample sizes are kept small to allow for in-depth exploration of phenomena [36]; this also takes into consideration the laborious nature of case-by-case analysis [37]. We will use the interpretative phenomenological analysis (IPA). IPA makes sense of the participant's experiences by seeking to understand the cognitive, affective, linguistic, and physical being while maintaining the researcher as an integral part of the sense-making process [37,38]. This methodology is best used in studies where the objective is to explore the meaning behind the experiences of participants. IPA is an especially fitting research approach when the researcher intends on asking complex, broad, and open-ended questions [37], as is the case in this research proposal. In keeping with the open-ended nature of qualitative research, this method allows the researcher to explore the research question in a flexible nonprescriptive manner, thus facilitating a more thorough exploration [38]. Although quantitative methodologies can supply information on the *what* aspect of the phenomenon, they do not aim to develop understandings about personal experiences and *why* and *how* phenomena occur. The choice to use qualitative methodology for this research was based on the need to better understand the interactions of important factors related to the phenomenon under study [39]. The methodology was also chosen because there is a need to better understand how the phenomenon is being experienced and understood by those who go through it personally. Quantitative methodologies, although

valuable, are not appropriate to explore how individuals experience a phenomenon. Statistical methods may provide an estimate about how many individuals have been impacted by suicide or how many individuals who have suicidal ideation access the health care system, but they do not explain how suicide impacts different individuals personally and how different factors interact. The explanations happen through the interpretation of the data. As stated, statistical data do not shed light on the *why* or *how* of situations. A common example used to caution against interpreting correlations is as follows: "there is a correlation between eating ice-cream and drownings." One individual might say, "eating ice-cream causes drownings!" Another would say, "in the summer-time, more individuals like to eat ice-cream. People also tend to swim more in the summer and may drown. Perhaps someone ate a lot of ice-cream before swimming and as we know, eating immediately before swimming may increase your risk of drowning." Although researchers can theorize about interpretations of quantitative results, proponents of qualitative research hold that it is best to go to the sources and ask for explanatory stories in an explorative manner.

Ethics and Operational Approval

The study will be conducted in accordance with the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (Canadian Guidelines). Written informed consent will be obtained from each participant. The study has received ethical clearance from Health Ethics Research Board of the University of Alberta (reference number Pro00086420)**.**

Participants

About 6 to 8 key informants will be recruited to participate in the study through purposive sampling.

Participants who meet the following criteria will be approached and invited to participate in the study: aged 18 years or older; English speaking; have the ability to give informed consent; have a close family member who has died by suicide (eg, spouse, parent, child, sibling, and grandparents); one member per family of suicide victim for interviews; a minimum of 3 months has passed since their family member has died to avoid the acute bereavement period; had regular contact with their family member, before their suicide, such that they are reasonably aware of their interaction with the health care system.

Recruitment

The following steps outline how participants will be identified for the study:

- Recruitment poster (Multimedia Appendix 1) would be posted in all the recruitment sites, which directs participants to the research coordinator, should they express interest in participating in the study.
- Posters would be shared mainly with the Canadian Mental Health Association (CMHA) in Edmonton Zone.
- The Executive Director for the Edmonton Zone (CMHA) will distribute the recruitment poster to their contacts, including groups run by the organization, and potentially use social media as a platform to recruit, in Alberta.
- The recruitment poster will also be shared with the Centre for Suicide Prevention for distribution to their contacts and on social media.
- The researcher coordinator will promote the study at a Suicide Prevention and Awareness Booth at a Mental Health Walk in Edmonton in June 2019.
- This process will continue until 6 to 8 participants have been recruited.
- During analysis of the data, if saturation has not been achieved, we will open up the recruitment until fulfilling saturation.

Data Collection

The key informant interviews will comprise an in-person semistructured interview with each participant. Interviewers will be graduate students trained in qualitative interviewing and will be supervised by the research coordinator. The interview will span 1.5 to 2 hours and will allow for a certain degree of flexibility in the types of questions asked, thus providing rich and contextualized understanding while also creating some consistency across participant interviews. More specifically, an interview protocol has been developed, and interviewers will aim to ask all the questions. However, they may change the order of the questions if participants lead the conversation in different ways. Interviewers may also prompt individuals when needed with statements such as "tell me more" and "can you tell me a story about a time when…" To facilitate this exploration, we will adopt what is known as a *funneling technique* to sequence the topics covered, starting first with the more general topics and then moving to the more salient or emotionally laden topics [37]. Using this technique, the interview will unfold in a logical and relaxed fashion while taking into consideration the sensitive nature of the subject matter. Saturation will be reached when no new information is added to the interview. Data saturation can be conceptualized in different ways: individual-level data saturation and group-level data saturation. During the individual interviews, the researcher needs to continue to probe until they feel they have a good understanding of the individual's experiences; this is one level of saturation. During the group-level analysis, saturation is considered to be reached when no new research codes (or themes) are being developed when nothing new is coming up to support a concept. When the information that researchers are getting from participants is becoming repetitive or redundant, then researchers argue that data saturation has been reached [40]. Both levels of saturation will be considered in the research process.

The interview will be audio recorded and then later transcribed verbatim. Interviews will take place in 3 main AHS sites according to the patient preference. Data from all participants will be compared and contrasted only after each participant's experience has been analyzed and considered on its own.

Data Analysis

The primary aim of data analysis will be to discover common themes according to individual experience and across participants. In keeping with traditional forms of content analysis, we will begin by reading and rereading the transcribed interviews, known as the preliminary exploratory analysis phase

[41], while considering possible concepts or themes. The purpose of this phase is to begin to develop a sense of the data as a whole. We will then begin coding the data, a process whereby the researcher makes sense of the data by dividing text into sections. We will initially code the transcript data at a relatively low level of abstraction by looking for common concepts as seen in individual interview data as well as across participants. We will proceed to a higher level of abstraction by grouping the codes into common themes and subthemes, a process known as *clustering* [37]. This process is iterative and involves many revisions, checking back to ensure that the proposed themes fit with the transcription data. Themes will then be inputted in a table, tracking the overarching theme(s), subordinate themes, and where the theme emerges in the transcribed data (ie, page number). From this point, certain themes will be selected based on importance (how the theme adds to the overall account) and how it adds to the richness of data. The final stage of data analysis will include writing up the themes in the form of a narrative using transcribed data to account for and justify the coding of certain themes. The final analysis will be broken into 2 sections: the findings, where a description of each theme and the corresponding quotes will be presented, and the discussion section, where we will interpret the findings in light of the extant literature. The demographic data to be collected as part of the interview would identify the relationship between the study participants and the persons who died by suicide. These data would allow for the identification of responses and matching as well as comparison with potential confounding factors such as age, sex, and relationship

Evaluation of the Goodness of Qualitative Research

Credibility and confidence are essential considerations when addressing the area of qualitative enquiry. This is because qualitative enquiry is intrinsically interpretive, and the investigators are as much a part of the study as the participants [41]. For the purpose of this study, and similarly to our approach in a concurrent borderline personality disorder study being undertaken by the team, we will enhance credibility and confidence by way of member checking and external appraisals. Member checking necessitates the investigator check with participants with regard to the validity of findings by asking clarifying questions used to enhance and deepen the interpretations, as they arise in the interview with the participant. External appraising considers the estimations of another person, for instance, a coinvestigator or research supervisor, aimed at reviewing codes and themes in search of continuity and validity [41]. The study findings will also be thoroughly and carefully evaluated for consistency, persuasiveness, comprehension, and practicality [42,43].

Results

We anticipate that recruitment for the study would begin in April 2019, and we expect the study findings to be available within 12 months. We expect the findings to shed light on the experiences of suicide victims and the experiences of their family members with the health care system. The findings will be disseminated at several levels, including patients, family members, practitioners, academics, researchers, and health care organizations.

Discussion

Expected Findings and Implications

Both those who experience suicidal ideation and those close to them can offer their perspectives into the experience. When a relative dies by suicide, family members can offer valuable insight into their relatives' interaction with the health care system. Similarly, understanding family members' own experiences with the health care system is also valuable. In a previous study, family members noted that the most significant barrier to identifying and managing suicide in primary care is the brevity in interactions with physicians [32]. In another study, family members reported that despite the presence of warning signs, their relatives were overlooked by health care providers in the lead-up to their suicide [33]. Another study of elderly people who died by suicide found them to have a general distrust in the health care service [34]. Despite the negative views expressed in these studies about the health care system, one study reported on the compassionate care their relative received by the health care providers [32], thus underscoring the potential for health care interactions to serve as a means of support among suicidal individuals. Reflecting on their relatives' death by suicide would understandably highlight the perceived inadequacies and potential strengths of the health care system. Family members may feel excluded from treatment information [33] and experience difficulty in seeking help outside the social network [35]. This is especially poignant, given that family members may continue to interact with the health care system after the death of their loved one [44-47]. Although it is positive to see that family members are consulted, there remain gaps in how patients and families perceive their care and the impact it may have on their health outcomes. What appears to be needed is an understanding of the experiences of death by suicide in the context of the local health care systems. In light of the above, family members who share their perspectives on their relatives' interaction with the health care system, and their own, offer valuable insight, which could potentially inform system policy and enhancements as well as reduce suicide rates in Alberta and beyond.

Conclusions

Our study would be the first in Alberta to examine how suicide victims and their family members interacted with the health care system. Our study results may inform practice, policy, and further research in Alberta, Canada, and internationally. They may shape how members of the health care system respond to people who are at risk of suicide and their families.

Acknowledgments

This work is being funded by the Edmonton Mental Health Foundation.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Recruitment poster. Participants needed: adults who have lost a family member to suicide.
[PDF File (Adobe PDF File), 83KB - resprot_v8i8e13797_app1.pdf]

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Abbreviations

AHS: Alberta Health Services
CMHA: Canadian Mental Health Association
IPA: interpretative phenomenological analysis
QAR: Quality Assurance Review

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Protocol

Aortic Stenosis Prognostication in Patients With Type 2 Diabetes: Protocol for Testing and Validation of a Biomarker-Derived Scoring System

Suresh Giritharan[1,2], MBChB, MRCS; Felino Cagampang[1], PhD; Christopher Torrens[1], PhD; Kareem Salhiyyah[2], PhD; Simon Duggan[2], PhD; Sunil Ohri[2], MD

[1]Institute of Developmental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

[2]Wessex Cardiac Centre, University Hospitals Southampton, Southampton, United Kingdom

Corresponding Author:
Suresh Giritharan, MBChB, MRCS
Institute of Developmental Sciences
Faculty of Medicine
University of Southampton
216 Tremona Road
Southampton, SO16 6HW
United Kingdom
Phone: 44 02380777222
Email: suresh.giritharan@gmail.com

Abstract

Background: Type 2 diabetes mellitus (T2DM) has been established as an important independent risk factor for aortic stenosis. T2DM patients present with a higher degree of valve calcification and left ventricular dysfunction compared to patients without diabetes. This may be due to an increase in incidence and severity of myocardial fibrosis. Currently, there is no reliable method of determining the optimal timing of intervention for a patient with asymptomatic aortic stenosis or predicting when a patient will become symptomatic. Research into serum biomarkers to predict subclinical onset and track progression of aortic stenosis is hampered by the multimodal nature of the pathological processes ultimately responsible for aortic stenosis.

Objective: The aim of this study is to prove that an approach using a combination of serum biomarkers and the echocardiographic parameter global longitudinal strain (GLS) can be used to establish baseline status of fibrocalcific aortic valve disease, predict rate of progression, and quantitatively assess any regression of these processes following aortic valve replacement in patients with T2DM.

Methods: Validated serum biomarkers for the separate processes of calcification, inflammation, oxidative stress and fibrosis can be used to quantify onset and rate of progression of aortic stenosis. This, in combination with the echocardiographic parameter GLS, can be compared with other objective investigations of calcification and fibrosis with the aim of developing a quick, noninvasive one-stop assessment of aortic stenosis in patients with T2DM. The serum biomarkers BNP (B-type natriuretic peptide), Gal-3 (Galectin-3), GDF-15 (growth differentiation factor-15), sST2 (soluble suppression of tumorigenicity 2), OPG (osteoprotegerin), and microRNA 19b and 21 will be sampled from patients undergoing aortic valve replacement (with and without T2DM), patients with T2DM but without aortic valve disease and healthy volunteers. These patients will also undergo computed tomography (CT) scans for calcium scoring, magnetic resonance imaging (MRI) to quantify myocardial fibrosis, and myocardial strain imaging with speckle-tracking echocardiography. Samples of calcified native aortic valve and a biopsy of ventricular myocardium will be examined histologically to determine the quantity and distribution of calcification and fibrosis, and the secretome of these tissue samples will also be analyzed for levels of the same biomarkers as in the serum samples. All patients will be followed up with in 3 months and 12 months for repeat blood sampling, echocardiography, and CT and MRI imaging to assess disease progression or regression. The results of tissue analysis and CT and MRI scanning will be used to validate the findings of the serum biomarkers and echocardiographic assessment.

Results: Using all of the information gathered throughout the study will yield a ranking scale for use in the clinic, which will provide each patient with a fibrocalcific profile. This can then be used to recommend an optimal time for intervention.

Conclusion: A reliable, validated set of serum biomarkers combined with an inexpensive bedside echocardiographic examination can now form the basis of a one-stop outpatient-based assessment service, which will provide an accurate risk assessment in patients with aortic stenosis at first contact.

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KEYWORDS

aortic stenosis; myocardial fibrosis; type 2 diabetes mellitus; biomarkers; ventricular remodelling; aortic valve replacement

Introduction

Aortic stenosis (AS) remains the most common valvular disease in adults, with a prevalence of 5% in people over the age of 65 years [1]. While type 2 diabetes mellitus (T2DM) has been established as an independent risk factor for this disease, little is understood about the precise nature of this association. Initially, it was attributed to the same inflammatory processes involved in the development of coronary artery disease (CAD) [2]. This theory is now in doubt as modulation of coronary risk factors do not reduce the incidence of aortic stenosis in these patients [3]. Advanced stages of AS warrants surgical aortic valve replacement (AVR) [4]. Despite the aid of echocardiographic parameters allowing for delineation of mild, moderate and severe aortic stenosis, the single prevailing indication for surgical intervention is the severity of symptoms [5].

The physiological narrowing of the valve which limits the outflow of blood is the end result of a complex array of cellular mechanisms that culminate in two distinct but intertwined pathological processes: calcification and fibrosis [6]. These mechanisms are also responsible for the stiffening and loss of elasticity of ventricular muscle due to abnormal deposition of collagen, a process termed myocardial fibrosis [7]. Currently, there is no reliable method of ascertaining if, or how soon, a patient with asymptomatic AS will become symptomatic. Given that these cellular modulations occur insidiously_presumably over a duration of time prior to the onset of symptoms_it is likely that the ventricular myocardium will have sustained a degree of fibrotic insult prior to identification of the need for aortic valve replacement. This current approach to guiding therapy has the potential pitfall of depriving these patients of the therapeutic effect of early reverse remodeling of the ventricle. This is a process where stiffened, fibrotic myocardium has the potential to regress to its initial elastic, nonhypertrophic state once ventricular afterload (secondary to stiffening by calcification and fibrosis) is reduced by AVR [8].

As the presence of T2DM has been shown to accelerate the progression of aortic stenosis, it is not unreasonable to conclude that patients with T2DM who develop severe aortic stenosis warranting AVR may have more advanced underlying myocardial fibrosis. This may not be amenable to the beneficial phenomenon of reverse-remodeling following replacement of the valve; such T2DM patients may benefit from early AVR. A reliable strategy of tracking the cadence of disease progression and susceptibility to reverse-remodeling is therefore necessary, as this would optimize timing of surgery for high-risk patients. We hypothesize that a method utilizing biomarkers for the tracking of underlying cellular processes culminating in aortic stenosis shows promise in achieving this.

Methods

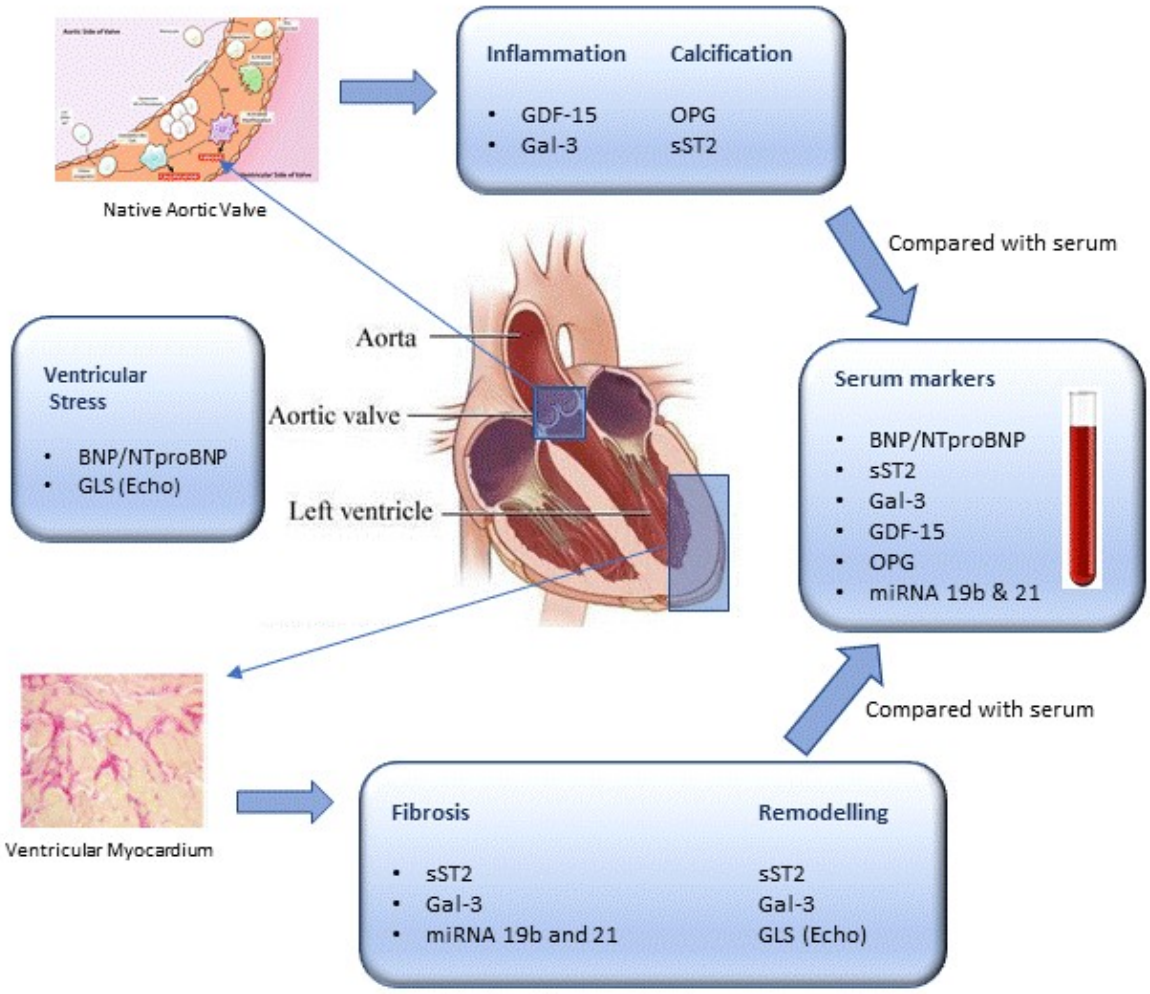
Presentation of the Hypothesis

The identification of a specific serum biomarker which can provide both an insight to the static state of a pathological process and track its progression (and subsequent regression following appropriate intervention) has proved challenging. This is due to the multimodal nature of the mechanisms which ultimately culminate in stiffening of the aortic valve. However, as a result of various studies of calcification and fibrosis in the heart, there is consensus that four core subprocesses are synergistically responsible in achieving the endpoint of aortic stenosis: valve mineralization (calcification), local inflammation, oxidative stress and ventricular fibrosis [9]. Within the domain of each subprocess, several promising biomarkers have shown acceptable specificity [10]. Here, we hypothesize that an approach using a combination of serum biomarkers and the echocardiographic parameter global longitudinal strain (GLS), a functional marker which will be discussed later, can be used to establish baseline status of fibrocalcific aortic valve disease, predict rate of progression and quantitatively assess any regression of these processes following AVR in patients with T2DM.

Serum Biomarkers

Figure 1 provides an overview of the site of expression of relevant biomarkers. BNP (B-type natriuretic peptide), and its prohormone NT-proBNP (n-terminal pro brain natriuretic peptide), are neurohormones and markers of stretching of the heart muscle. BNP is secreted by cardiomyocytes following volume and pressure changes in the left ventricle. NT-proBNP in particular demonstrates an incremental relationship with the severity of aortic stenosis. Although in isolation this biomarker is unable to distinguish between the pathologies of calcification and fibrosis, it is valuable in ascertaining the cumulative consequence of ventricular dysfunction and has predictive value [11].

Figure 1. Location of biomarkers of inflammation, calcification, fibrosis, ventricular stress and remodelling in aortic valve and myocardial tissue which will be compared to levels in serum. BNP, Brain Natriuretic Peptide; Gal-3, Galectin-3; GDF-15, Growth Differentiation Factor 15; GLE, Global Longitudinal Strain; miRNA, micro ribonucleic acid; OPG, Osteoprotegerin; sST2, Soluble ST2.



sST2 (soluble suppression of tumorigenicity 2) is a member of the IL1 (interleukin-1) receptor family and is a marker of ventricular remodeling. sST2 levels increase with myocardial stress and have been demonstrated to correlate quantitatively with myocardial ischemia and heart failure. It is of particular use as it correlates with echocardiographic assessment of diastolic dysfunction and has been demonstrated to correlate with heralding the onset of new symptoms in previously asymptomatic aortic stenosis patients. High levels of sST2 are an independent predictor of mortality following aortic valve replacement surgery [12].

Gal-3 (Galectin-3) is a beta-galactoside-binding lectin and a marker of inflammation and fibrosis of the myocardium, but it is also responsible for other processes such as regulating T-cell function and apoptosis. Gal-3 has a limited role in predicting progression of ventricular stiffening as it is also upregulated in other conditions such as renal dysfunction. However, when considered in tandem with BNP, it has shown to have significant predictive properties in the progression of heart failure [13].

The microRNAs 21 and 19b are specific small RNAs that are 19-25 nucleotides long which are postulated to regulate gene expression related to various cellular mechanisms underpinning cardiovascular function. Although assessment of these micro-RNAs is still in early stages, microRNA-21 has shown good correlation with myocardial fibrosis. MicroRNA-19b has shown promise in determining increased myocardial collagen cross-linking in patients with aortic stenosis [14].

GDF-15 (growth differentiation factor-15) is a stress-responsive cytokine that is sensitive to inflammatory changes and apoptosis. It is abundant in cardiomyocytes, adipocytes and macrophages and has demonstrated good predictive value in heart failure, vascular calcification and endothelial dysfunction. Like Gal-3, it is upregulated in renal dysfunction and additionally in obesity and insulin-resistant states such as diabetes. Although recent work has established GDF-15 as a useful prognostic and diagnostic marker of cardiometabolic disease in patients with diabetes, reference ranges correlating to severity have not yet been established [15].

OPG (osteoprotegerin) is a member of the tumor necrosis factor receptor family and is expressed in early arteriosclerotic lesions and vascular smooth muscle cells. It has an important role in neocalcification, acting as a decoy receptor by binding to the RANKL (receptor activator kappa-B ligand) nuclear factor and inhibiting the receptor activity of RANK (receptor-activated kappa-B). This thus inhibits osteoclastic activity, which ultimately leads to calcification. Modulation of this pathway

by the action of anti-Ghrelin antibodies suppressing OPG expression is of particular interest in seceding calcification [16].

Global Longitudinal Strain as a Complimentary Functional Marker

Speckle-tracing echocardiography is a relatively novel echocardiographic technique which has been shown to be more sensitive than conventional assessments of ejection fraction (EF) in the assessment of minute, regional wall motion abnormalities (RWMA) and left ventricular function. It correlates well with the presence and magnitude of myocardial fibrosis when compared alongside cardiac magnetic resonance, as assessed through T1-mapping and late gadolinium enhancement as quantification techniques. This noninvasive imaging modality can serve as an additional functional marker alongside the serum biomarkers mentioned above in the assessment of severity of aortic calcification and in the evaluation of reverse-remodeling postoperatively [17].

Testing the Hypothesis

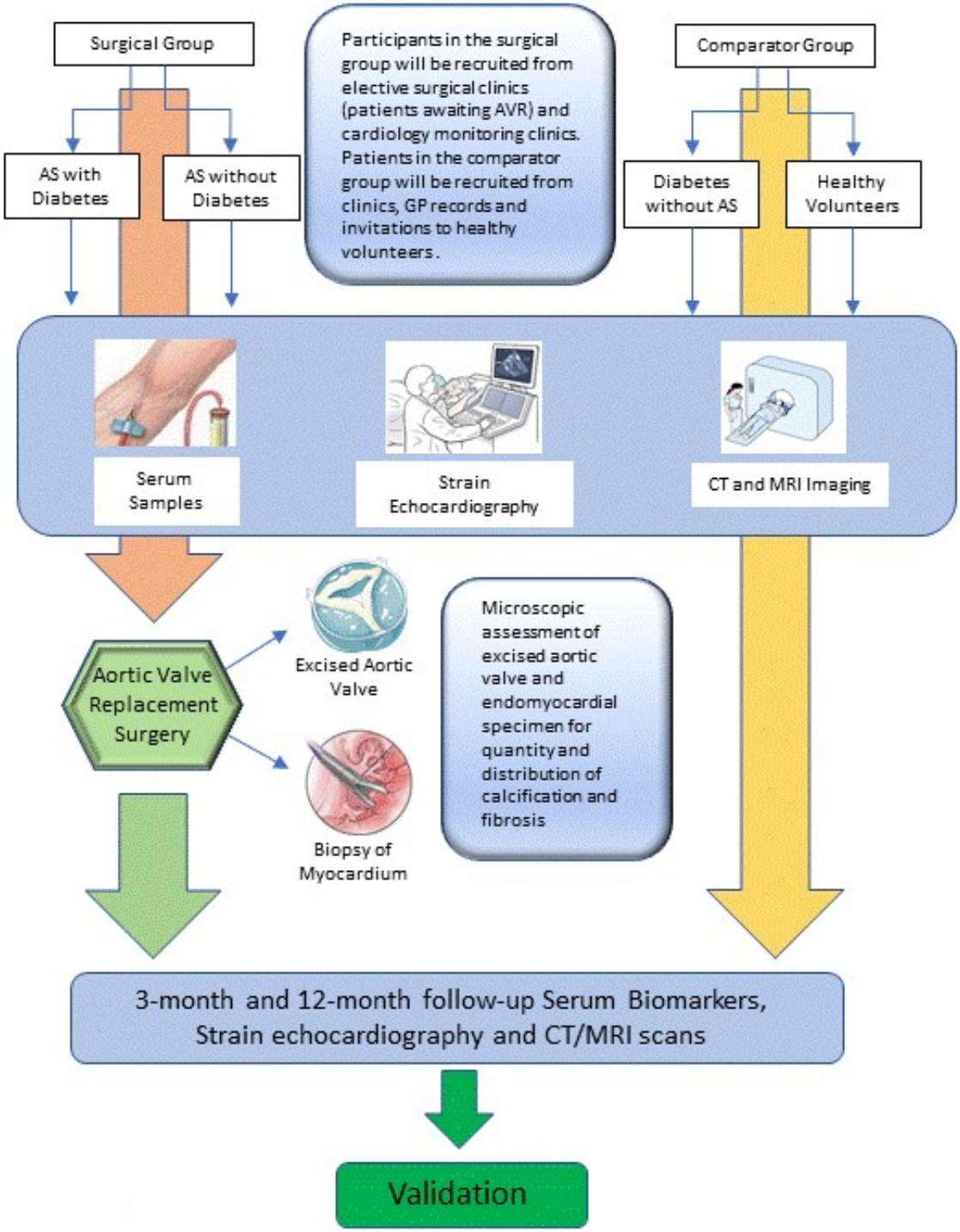
Figure 2 outlines the process of biomarker testing in the relevant patient cohorts. Gold standard assessments of aortic valve calcification and myocardial fibrosis are direct microscopic inspection of the excised aortic valve, following AVR, and a biopsy specimen of the ventricular myocardium, respectively [18]. Noninvasive imaging techniques done preoperatively, Computed Tomographic (CT) Calcium Scoring for aortic valve calcification and Late Gadolinium Enhancement magnetic resonance imaging (MRI) for myocardial fibrosis, will corroborate the findings of direct inspection. These results will be used to calibrate serum biomarkers and echocardiographic findings for the subset of patients with severe AS undergoing surgery.

Healthy volunteers and patients with milder, asymptomatic forms of the disease will be recruited from outpatient cardiology surveillance clinics to undergo serum biomarker sampling and strain echocardiograms. They will then undergo CT and MRI scans to investigate the relevance of these markers against objective imaging findings. This will enable the establishment of baseline levels in healthy volunteers and grading of the markers in mild, moderate and severe forms of disease.

Finally, postoperative patients will be followed up with in 3 months and 12 months following surgery where they will once again undergo serum biomarker sampling and strain echocardiography to assess for evidence of reverse-remodeling. Again, CT scans for calcium scoring and MRI scans will be repeated to validate the significance of any downregulation of these biomarkers.

The combination of biomarker and echocardiographic data encompassing the entire spectrum of the disease from healthy volunteers to patients with severe disease as well as disease monitoring in postoperative patients will yield a ranking scale for use in the clinic. This scale, once validated for reproducibility in an appropriately powered study, will provide each patient with a fibrocalcific profile which can then be used to recommend an optimal time for intervention.

Figure 2. Testing the hypothesis. Preoperative serum biomarkers and echocardiography will be compared to CT and MRI imaging to quantify calcification and fibrosis. Samples of valve and myocardial tissue will be examined for calcification and fibrosis and compared to serum biomarkers. Follow-up investigations will assess if upregulation or downregulation of biomarkers show reliable clinical correlation with disease progression or regression. AS: aortic stenosis; AVR: aortic valve replacement; CT: computed tomography; MRI: magnetic resonance imaging.



Results

Enrollment has not commenced for this study. Ethical approval was obtained from South Central - Hampshire A Research Ethics Committee (United Kingdom – REC: 18/SC/1062, IRAS: 024397). Funding was obtained from the Wessex Heart Surgery Charitable Fund (registered charity #1051543).

Discussion

A reliable, validated set of serum biomarkers combined with an inexpensive bedside echocardiographic examination can now form the basis of a one-stop outpatient-based assessment service in providing an accurate risk assessment in patients with AS at first contact. In patients with diabetes, the role of such a service can be expanded to an essential screening service given the less favorable prognosis of aortic stenosis in this demographic.

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Authors' Contributions

SG is responsible for the conceptualization of the hypothesis. SO provided guidance on the choice of biomarkers. FC and CT recommended appropriate laboratory techniques for analysis of the biomarkers. KS and SD designed the experimental model for testing the hypothesis. All authors provided final critical review of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AS: aortic stenosis
AVR: aortic valve replacement
BNP: brain natriuretic peptide
CAD: coronary artery disease
CT: computed tomography
EF: ejection fraction
Gal-3: Galectin 3
GDF-15: growth differentiation factor 15
GLS: global longitudinal strain
IL1: Interleukin-1
MRI: magnetic resonance imaging
NT-proBNP: n-terminal pro brain natriuretic peptide
OPG: osteoprotegerin
RANKL: receptor-activated kappa B ligand
RNA: ribonucleic acid
RWMA: regional wall motion abnormality
sST2: soluble suppression of tumorigenicity 2
T2DM: type 2 diabetes mellitus

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Protocol

Safety and Efficacy of Bis-Glyceryl Ascorbate (Amitose DGA) to Prevent Hand-Foot Skin Reaction in Patients With Renal Cell Carcinoma Receiving Sunitinib Therapy: Protocol for a Phase I/II, Uncontrolled, Single-Arm, Open-Label Trial

Kazuhiro Yamamoto[1], PhD; Takeshi Ioroi[1], PhD; Kenichi Harada[2], MD, PhD; Satoshi Nishiyama[3], MD, PhD; Chikako Nishigori[3], MD, PhD; Ikuko Yano[1], PhD

[1]Department of Pharmacy, Kobe University Hospital, Kobe, Japan

[2]Department of Urology, Graduate School of Medicine, Kobe University, Kobe, Japan

[3]Division of Dermatology, Department of Internal Related, Graduate School of Medicine, Kobe University, Kobe, Japan

Corresponding Author:
Kazuhiro Yamamoto, PhD
Department of Pharmacy
Kobe University Hospital
7-5-2, Kusunoki-cho
Chuo-ku
Kobe, 650-0017
Japan
Phone: 81 78 382 6659
Email: yamakz@med.kobe-u.ac.jp

Abstract

Background: Hand-foot skin reaction (HFSR) is a serious side effect induced by multiple-tyrosine kinase inhibitors (TKIs). HFSR can cause treatment interruption or decreased dosing. HFSR also markedly decreases quality of life and is associated with the therapeutic efficacy of multiple-TKIs. Therefore, the management and prevention of HFSR is an important issue; however, an effective method for its prevention has not been established. Specific ascorbic acid derivatives can reverse multiple-TKI-induced keratinocyte growth and pathological changes in vitro.

Objective: This study was designed to evaluate the safety of bis-glyceryl ascorbate (Amitose DGA), a novel, hydrosoluble, and moisturizing ascorbic acid derivative, in patients with renal cell carcinoma (RCC) receiving sunitinib therapy. This study was also designed to evaluate Amitose DGA's preventive efficacy for sunitinib-induced HFSR.

Methods: This is a Phase I/II, single-center, uncontrolled, single-arm, open-label trial. We will recruit a total of 30 patients with RCC receiving sunitinib therapy, with a 2-week-on and 1-week-off schedule. The participants will apply Amitose DGA-containing cream over both palmar and plantar surfaces within two treatment cycles (ie, 6 weeks) of sunitinib in combination with a general moisturizing agent, in addition to standard-of-care processes. Safety assessments will include dermatological abnormalities, clinical laboratory tests, and incidence of adverse events. Efficacy assessments will include development of HFSR and therapeutic outcomes associated with sunitinib.

Results: Recruitment to the study began in August 2017 and is ongoing in Japan. To date, 21 subjects have been recruited. Study completion is expected in 2021.

Conclusions: This is the first clinical study of Amitose DGA-containing cream in patients with RCC who are receiving sunitinib therapy. The single-center, single-arm, open-label design was selected to maximize subject exposure and increase the likelihood of achieving our study endpoints. The results will provide valuable and preliminary evidence of the effects of Amitose DGA-containing cream on HFSR.

Trial Registration: UMIN Clinical Trials Registry UMIN000027209; https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000031174

International Registered Report Identifier (IRRID): DERR1-10.2196/14636

(JMIR Res Protoc 2019;8(8):e14636) doi:10.2196/14636

KEYWORDS

hand-foot skin reactions; renal cell carcinoma; tyrosine kinase inhibitors; ascorbic acid derivative

Introduction

Background

In recent years, several types of novel multiple-tyrosine kinase inhibitors (TKIs) against renal cell carcinoma (RCC) have been developed and applied in clinical practice settings [1]. Sunitinib, a multiple-TKI, is an especially important first-line therapy option for patients with metastatic RCC and is the most commonly used agent in clinical settings [2,3]. However, multiple-TKIs can cause serious side effects, which might cause treatment interruption or decrease of dose [4,5]. Hand-foot skin reaction (HFSR) is one such side effect. HFSR is a common and characteristic adverse reaction to multiple-TKIs [6,7] and develops as hyperkeratosis and redness on the palmar and plantar surfaces [7-9]. These side effects can cause walking difficulties and depressed holding and gripping function by the hands, potentially decreasing quality of life; in addition, there is a well-known association between development of HFSR and the therapeutic efficacy of multiple-TKIs [10,11]. Therefore, the management and effective prevention of HFSR has the potential to improve quality of life and the therapeutic outcomes of multiple-TKI treatments [10,12]. Although multiple-TKI-induced HFSR is recognized as a serious problem in clinical practice, effective methods for prevention have not been established.

We recently reported on ascorbyl-2-phosphate magnesium (P-VC-Mg), a highly permeable ascorbic acid derivative; we found that it could relieve multiple-TKI-induced keratinocyte growth inhibition and pathological changes in human keratinocyte cells in a 3D skin model, mediating signal transducer and activator of transcription 3 phosphorylation levels [13,14]. This report suggested that specific ascorbic acid derivatives can prevent multiple-TKI-induced HFSR. Because ascorbic acid derivatives are widely used within cosmetic preparations, it may be possible to establish additional safety parameters.

Bis-glyceryl ascorbate (Amitose DGA) is a novel hydrosoluble and moisturizing ascorbic acid derivative produced by binding ascorbic acid to glycerin. It is easily formulated as an emulsion and gel cosmetic because it is nonionic and has higher permeability and stability compared to other ascorbic acid derivatives. Our preliminary investigation used various ascorbic acid derivatives for keratinocyte growth inhibition with sunitinib. Amitose DGA showed the highest preventive effects among all the products examined, including P-VC-Mg. This effect was attributable to higher cellular translocation and environmental stability of Amitose DGA. There are various reports about the anti-inflammatory effects of ascorbic acid derivatives in healthy or diseased skin and keratinocytes [15-17]; however, its effects on HFSR induced by anticancer agents have not been reported. In spite of this, we consider Amitose DGA to be a strong candidate for HFSR prophylaxis.

Study Objectives

The primary objectives of this study are to evaluate the dermatological safety of Amitose DGA in patients with RCC who are receiving sunitinib therapy (Phase I) and to determine its prophylaxis efficacy in sunitinib-induced HFSR (Phase II). The secondary objectives are as follows:

1. Evaluate hematological abnormality of Amitose DGA-containing cream
2. Evaluate the effects of Amitose DGA-containing cream on severe sunitinib-induced HFSR
3. Evaluate the effects of Amitose DGA-containing cream on therapeutic outcomes related to sunitinib

Methods

Study Design

This study was designed to verify whether Amitose DGA safely and effectively prevents multiple-TKI-induced HFSR. This is an ongoing Phase I/II, single-center, uncontrolled, single-arm, open-label clinical trial to evaluate the safety and efficacy of Amitose DGA-containing cream as a prophylaxis for sunitinib-induced HFSR. Figure 1 summarizes the study design.

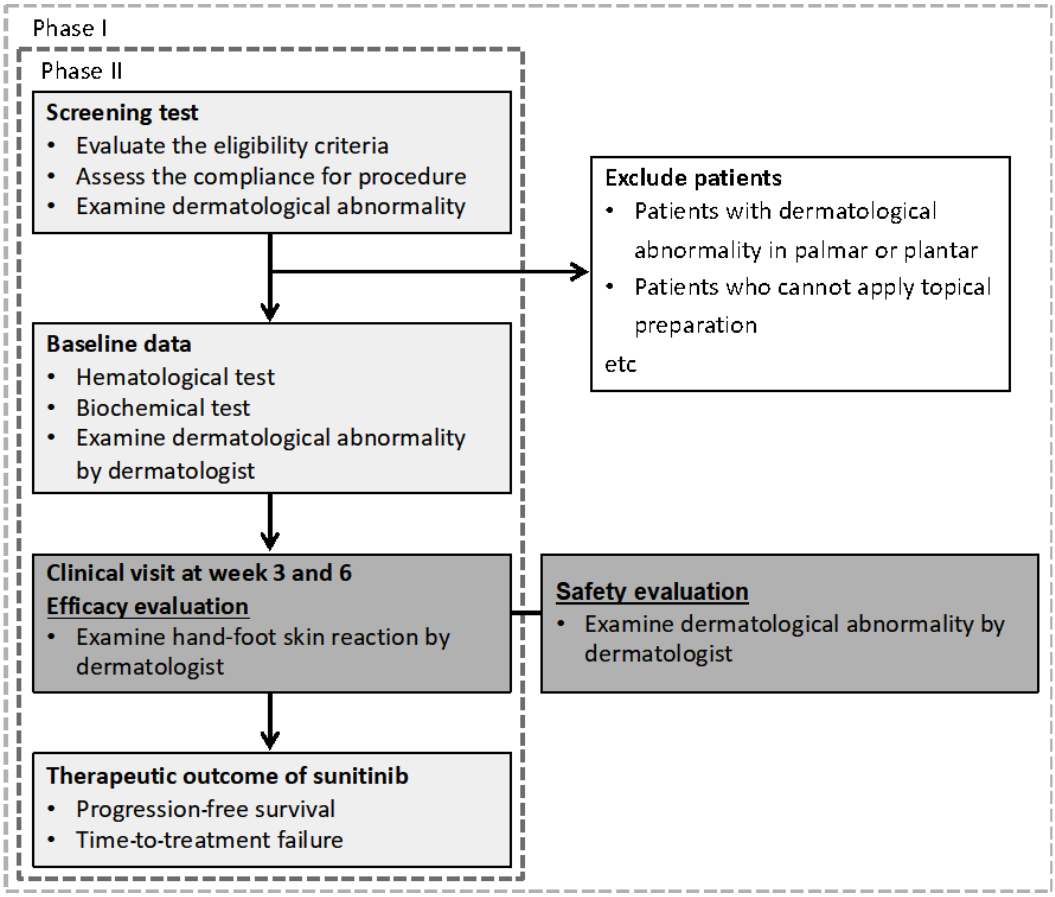
Study Location and Population

Subjects are being recruited from Kobe University Hospital, Kobe, Japan. The population of this study includes patients with RCC who are receiving sunitinib therapy at the hospital.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee at Kobe University Hospital (approval number: 290015) on August 22, 2017. Each participant will sign an informed consent form, which is worded in lay terms, following a comprehensive explanation of study procedures by a research collaborator; study-related risks and benefits will also be explained before participating in the study. To maximize the opportunity for free and informed consent, while respecting privacy and confidentiality, the informed consent process will take place privately. Potential participants will not be invited to join the study if the clinical research coordinator is not able to adequately explain the study and obtain informed consent. The study will be conducted in compliance with the protocol; regulatory requirements; Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Japanese Ministry of Health, Labour and Welfare; and the ethical principles of the latest version of the Declaration of Helsinki. Each substantial protocol amendment will receive approval by the Ethics Committee prior to implementation.

Figure 1. Flowchart of the study design.



Inclusion and Exclusion Criteria

We will include individuals capable of providing informed consent, aged 20 years or older, with histologically diagnosed RCC, receiving sunitinib therapy, with or without prior molecular targeted therapy, and before or after nephrectomy. All patients have an Eastern Cooperative Oncology Group Performance Status of 0-2 and are expected to survive for more than 12 weeks at screening. Finally, all the included patients will be determined to exhibit higher compliance for applying the investigational cream, attending clinical visits, undergoing laboratory tests, and keeping a personal dairy based on the study protocol. We will exclude patients with dermatological abnormalities of the palmar or plantar surfaces; those who use topical medications on the palmar or plantar surfaces, except for heparinoid or urea-containing cream; those who are unable to apply the heparinoid or urea-containing cream to the palmar or plantar surfaces; those with grade 1 or higher HFSR based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, at the start of sunitinib therapy; and those with active infections requiring treatment. We will also exclude patients with severe liver injury (ie, alanine aminotransferase ≥5 × upper limit of normal or 2 × individual baseline value); severe kidney injury (ie, serum creatinine level ≥2 × individual baseline value); and other patients who are determined to be inappropriate for study participation by the principal investigator.

Intervention

The participants will apply three fingertip units of Amitose DGA-containing cream all over both the palmar and plantar surfaces more than three times a day, within two treatment cycles (ie, 6 weeks) of sunitinib. They will also apply heparinoid or urea-containing cream as a standard preventive treatment for HFSR following application of the investigational cream. The participants will be instructed to apply the investigational cream to moist skin, such as when washing their hands or feet, during face washing, or after bathing. The participants will keep a personal diary to record the frequency of application of Amitose DGA-containing cream.

Study Outcomes

Primary Outcomes

The primary outcome of Phase I is development of dermatological abnormalities on the palmar or plantar surfaces, such as bullous dermatitis, dry skin, erythroderma, pruritus, purpura, rash maculopapular, skin hyperpigmentation, and skin hypopigmentation, within two cycles (ie, 6 weeks) of sunitinib therapy. The primary outcome of Phase II is development of grade 1 or higher HFSR within 6 weeks after the initiation of sunitinib therapy. These outcomes will be evaluated by qualified dermatologists.

Secondary Outcomes

The secondary outcomes of Phase I are hematological test abnormalities within the observation period. The secondary outcomes of Phase II are development of grade 2 or higher

HFSR within 6 weeks of sunitinib therapy, progression-free survival and time-to-treatment failure of sunitinib therapy, dermatological abnormalities of the palmar or plantar surfaces within the observation period, and development of grade 2 or higher HFSR within 3 weeks after completion of the investigational treatment. HFSR and dermatological abnormalities will be evaluated by qualified dermatologists.

Safety Endpoints

The safety endpoints are dermatological abnormalities in palmar or plantar surfaces, such as bullous dermatitis, dry skin, erythroderma, pruritus, purpura, rash maculopapular, skin hyperpigmentation, and skin hypopigmentation, as well as the frequency and severity of treatment-emergent adverse events. These adverse events have a cause-and-effect relationship with the investigational preparation, so we will also observe them over the whole treatment period.

Study Procedure

The study schedule is shown in Table 1. Screening tests will be performed within 1 week of obtaining informed consent and researcher confirmation of each patient's eligibility. Eligible patients will be enrolled via electronic case report forms (eCRFs).

Baseline data will be corrected beginning on the initial day of investigational cream usage. Patient-specific data (ie, sex, height, weight, concomitant diseases, medical history, prior chemotherapy, etc) and hematological and biochemical test data will be acquired from patients' electronic medical records as per usual care practice information. The baseline dermatological status of each participant will be determined from the screening test.

Patients will receive sunitinib for 2 weeks, followed by a 1-week interruption; therefore, the therapeutic cycle lasts for 3 weeks. The initial dosage of sunitinib will be 37.5 mg/day. The participants will begin treatment with Amitose DGA-containing cream simultaneously with the start of sunitinib therapy. Plasma concentrations of sunitinib will be measured 10-14 days after the start of sunitinib therapy, as per usual care practice. HFSR will be checked regularly by the hospital urologists during the first 2 weeks of sunitinib therapy; during this period, the patients will remain in hospital.

During week 3 and week 6 outpatient clinical visits, participants will receive dermatological examinations by a dermatologist. This examination will focus on dermatological abnormalities of the palmar or plantar surfaces to assess the safety of the Amitose DGA-containing cream in Phase I. The dermatologist will additionally assess the efficacy of the Amitose DGA-containing cream at these visits during Phases I and II.

Assessments

Hand-Foot Skin Reaction

HFSR grading will be done according to that for palmar-plantar erythrodysesthesia syndrome, as described by the National Cancer Institute CTCAE, version 4.0. The dermatologists will then determine the efficacy of the investigational preparation.

Table 1. Study schedule of events.

Study events and measurements	Screening phase	Treatment phase[a]						Posttreatment observation phase
	Within 1 week of obtaining informed consent	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 9
Sunitinib treatment		✓	✓		✓	✓		
Application of Amitose DGA cream		✓	✓	✓	✓	✓	✓	
Informed consent	✓							
Patients' backgrounds	✓							
Hematology[b] and biochemistry[c]	✓			✓			✓	
Sunitinib plasma concentration			✓					
Subjective symptoms	✓	✓		✓			✓	✓
Objective findings	✓	✓		✓			✓	✓
Dermatological examination	✓			✓			✓	
Adherence confirmation		✓	✓	✓			✓	
Observation of adverse events		✓	✓	✓	✓	✓	✓	✓

[a]The weeks listed correspond to the weeks after initiation of sunitinib.

[b]Hematology tests include red blood cell counts, hemoglobin, hematocrit, differential leukocyte counts, and platelet counts.

[c]Biochemistry tests include total protein, serum albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, lactase dehydrogenase, total bilirubin, direct bilirubin, creatine kinase, blood urea nitrogen, serum creatinine, uric acid, and serum concentrations of sodium, potassium, chloride, and calcium.

Compliance for Use of Investigational Preparation

Participant compliance will be monitored by the medical staff while the participants are inpatients. Once participants are transitioned to outpatient treatment, we will calculate a compliance ratio for the investigational preparation by determining instances of daily use, based on diaries kept by individual participants.

Dermatological Abnormalities

Dermatological abnormalities will be defined as grade 1 or higher dermatological events, including bullous dermatitis, dry skin, erythroderma, pruritus, purpura, rash maculopapular, skin hyperpigmentation, and skin hypopigmentation, as specified by the CTCAE, version 4.0. Dose-limiting toxicities will be defined as grade 2 or higher events. If dose-limiting toxicity is more than 40% and is confirmed to be causally connected to the use of the investigational preparation, the study will be terminated and will not advance to Phase II.

Plasma Concentration of Sunitinib

Plasma concentrations of sunitinib will be measured 10-14 days after the start of sunitinib therapy, as per usual care practice; the trough level of total concentration of sunitinib and its metabolite N-desethyl-sunitinib will be measured.

Progression to Sunitinib Therapy

Before the introduction of sunitinib, all patients will undergo radiological examinations, including computed tomography (CT) imaging of the brain, chest, and abdomen, or radionuclide bone scans, or both. Typically, tumor measurements are performed using CT every 8-12 weeks after initiating sunitinib therapy. All responses will be assessed by a treating physician based on the Response Evaluation Criteria in Solid Tumors, version 1.1.

Discontinuation of Study Subject Participation

Necessary testing will be carried out to assess the efficacy and safety of the Amitose DGA-containing cream if its use is permanently discontinued due to termination of subject participation in the study. Participants can be withdrawn from the study if their consent is withdrawn; if inadequacies are found after enrollment; if sunitinib therapy is determined to be unnecessary because of RCC resolution; or if the patient is unable to continue sunitinib therapy because of disease progression, complications, or adverse events induced by sunitinib or Amitose DGA-containing cream. Participation can be terminated in cases of pregnancy, noncompliance with the use of the investigational preparation (ie, compliance ratio less than 70%), if the study is discontinued, or if other issues emerge that warrant study discontinuation, according to the physician.

Statistical Plan

All analyses will be conducted using SPSS Statistics for Windows, version 24.0 (IBM Corp) or later. Interim analyses will be not performed.

Sample Size Calculation

Participants were enrolled in the Phase I cohort group until the sample size reached 5 patients, in the event that study discontinuation occurred before the use of the investigational preparation. The sample size for the Phase I study was primarily based on the extent of necessity and concernment. To limit the potency of intolerable adverse events, the investigational preparation is an ascorbic acid derivative, which is generally equivalent to cosmetic preparations; however, there are no practical safety data pertaining to the administration of Amitose DGA-containing cream to patients with RCC receiving sunitinib therapy. In this study, the safety of Amitose DGA has been confirmed by a cohort of 5 patients.

The sample size for the Phase II study will be 30 participants, in combination with the Phase I study sample (ie, 5 Phase I participants and 25 additional participants). In previous reports from our institution, HFSR of any grade (ie, grades 1-3) was 33.3%; HFSR of grade 3 was 2.2% among patients with metastatic RCC who were treated with a 2-week-on and 1-week-off sunitinib schedule [18]. Given that the investigational preparation can prevent up to 75% of grade 1-2 HFSR, we estimate that the frequency of HFSR of any grade (ie, grades 1-3) among patients using the investigational preparation will be 10%. In the case of this study, 25 participants will be needed to guarantee an alpha of .05 and 80% statistical power, with no continuity correction. Therefore, we aim to recruit 30 participants to mitigate potential exclusions from the analysis set.

Primary Analysis

In the Phase I study, the safety of the investigational preparation will be evaluated at the end of two cycles of sunitinib therapy. If 2 or more participants out of 5 (≥40%) show dose-limiting toxicities during the above safety evaluation period or if the fifth participant is confirmed to have started the investigational preparation normally, ongoing Phase I enrollment will stop. At this time, the study secretary and principal investigator will discuss and determine the safety of the investigational preparation, based on the eCRF that records safety evaluation data.

The null hypothesis of the Phase II study has been defined as the frequency of development of HFSR of any grade (ie, grades 1-3) is 33.3% [18], and the frequency of development of HFSR of any grade (ie, grades 1-3) in one sample is analyzed with a significance level of 5%.

Secondary Analysis

Secondary analysis on the efficacy of the investigational preparation throughout the whole observation period will be performed for additional discussion on the primary analysis, but multiplicity will not be adjusted in this analysis. Hypothesis testing will be performed with a two-sided 5% significance level and a two-sided 95% CI.

Logistic regression analysis, setting the development of HFSR as the dependent variable, will be performed by examining independent variables, including patient characteristics, sunitinib dose, and plasma concentrations of sunitinib, with a two-sided significance level of 5% and a two-sided 95% CI. Moreover, progression-free survival and time-to-treatment failure will be determined using the Kaplan-Meier estimate; medians and 95% CIs will be calculated.

We will carry out imputation for missing data by multiple imputation, as appropriate. Primary analyses will be performed by intention-to-treat analysis. Secondary analyses will consider per-protocol set, including participants who completed the treatment according to the scheduled protocol.

Pharmacovigilance and Data Monitoring

We will pay for the management of all serious adverse events suffered by subjects in the clinical trial and will compensate them or their families for injuries or deaths related to the study, using the clinical trial insurance coverage. All serious adverse events will be reported to the principal investigator within 24 hours of the trial investigator becoming aware of each event. Subsequently, the principal investigator will report each event to the ethics committee within 48 hours. All relevant information about any suspected or unexpected serious adverse reactions that occur during the study, particularly those that are fatal or life-threatening, will be reported as soon as possible, and no later than 7 days, to the appropriate authorities.

The principal investigator will designate a monitor to review individual subject safety data in an ongoing fashion and will monitor the data collected throughout the study, thus providing quality control for the study. Because of the small size of this study, an audit is not planned.

Privacy and Confidentiality

Both the eCRFs and the personal computer storing the eCRFs will be password protected. The computer will be stored in a secure location under the care of the study secretary, and the eCRFs will be destroyed after study completion. Privacy and confidentiality will be further secured by assuring that only deidentified data will be used in place of personal identifiers within all eCRFs.

Results

This study is ongoing. Recruitment to the study began in August 2017 and is ongoing in Japan. To date, 21 subjects have been recruited. Study completion is expected in 2021. The results of the study will be disseminated through one or more scientific papers and may also be presented at medical conferences. The datasets generated and the data analyzed during this study will be available from the corresponding author upon appropriate request after publication.

Discussion

HFSR is not a life-threatening side effect of multiple-TKIs but can drastically decrease quality of life and adherence to chemotherapy. This is the first clinical study of an Amitose DGA-containing cream in patients with RCC receiving sunitinib therapy. Moreover, this may be the first clinical study to use cosmetic preparations to determine dermatological adverse events induced by anticancer agents. This study will inform future, novel, prevention methods for HFSR.

We have reported the effects of ascorbic acid derivatives on keratinocyte toxicity induced by multiple-TKIs in vitro [13]. We verified these effects using an animal-testing alternative, consisting of a reconstructed human epidermal model in vitro. This methodological approach has also been used to evaluate dermatological adverse events [19-21]. Our experiment was conducted using similar methods; however, our results are preliminary and require further validation. Considering the evidence from our previous study, we aimed to evaluate both the effects of ascorbic acid derivatives alone on HFSR and the effects of combination therapy involving ascorbic acid derivatives and an existing standard-of-care prophylaxis.

The subjects of this study are patients receiving sunitinib therapy, not including other multiple-TKIs. We selected a single-arm, open-label design to maximize subject exposure and increase the likelihood of achieving study endpoints. Given our limited study population, the results of this study will be clear but the insights gleaned will be limited in their potential application.

Results from our previous study indicated that sunitinib-induced HFSR is likely to develop within 6 weeks of sunitinib initiation [22]. In this study, HFSR evaluated at weeks 3 and 6 was considered induced by sunitinib. Because sunitinib-induced HFSR also develops in latter phases, longer observation periods should be considered. Because adverse events related to sunitinib can cause dose reduction and interruption [23,24], the primary endpoint was set within two therapeutic cycles, considering study feasibility and clarity of results.

The exclusion criteria were established to assist with the safe and ethical performance of this study. These criteria differed from the exclusion criteria of a previous study, which reported on the frequency of HFSR with a 2-week-on and 1-week-off schedule of sunitinib conducted at our hospital [18]. The criteria for this study were set in order to compare the development of HFSR; we do not believe this will adversely affect subject recruitment.

Development of HFSR is associated with higher plasma concentrations of sunitinib [25-27]. Therefore, our secondary endpoints include the evaluation of plasma concentrations of sunitinib around day 10, as this time point is believed to represent steady-state concentrations [28].

This study will provide preliminary and valuable evidence to support the use of Amitose DGA in the prevention of HFSR. Amitose DGA may improve the pain and suffering caused by therapy with multiple-TKIs, while enhancing therapeutic outcomes.

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Authors' Contributions

KY conceived the study, drafted the study protocol, and drafted the manuscript. TI reviewed the study protocol and manuscript. SN, CN, and KH are running the study. IY reviewed the final manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

This study is supported with funding from Momotani Juntenkan Ltd (1-4-1, Uemachi, Chuo-ku, Osaka, 540-0005, Japan) to KY. The Amitose DGA-containing cream used in this study is provided by Momotani Juntenkan Ltd. The funder had no role in the study design and will not have any role during data analysis and interpretation or submission of results.

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Abbreviations

Amitose DGA: bis-glyceryl ascorbate
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
eCRF: electronic case report form
HFSR: hand-foot skin reaction
P-VC-Mg: ascorbyl-2-phosphate magnesium
RCC: renal cell carcinoma
TKI: tyrosine kinase inhibitor

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Protocol

Improving Mental Health in Pregnancy for Refugee Women: Protocol for the Implementation and Evaluation of a Screening Program in Melbourne, Australia

Jacqueline Anne Boyle[1], PhD, MPH&TM, FRANZCOG, MBBS; Suzanne Willey[1], RN, MN; Rebecca Blackmore[1], BaSocSci (Hons); Christine East[1], PhD, RN, MN, BApplSc, DApplSc; Jacqueline McBride[2], BAs; Kylie Gray[3], PhD; Glenn Melvin[3], PhD; Rebecca Fradkin[4], MBBS (Hons), FRACGP, DRANZCOG; Natahl Ball[5], MN, RN; Nicole Highet[6], PhD; Melanie Gibson-Helm[1], PhD, MRepSci, BSc (Hons), BCA

[1]Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[2]Monash Health Refugee Health and Wellbeing, Monash Health, Melbourne, Australia
[3]Centre for Developmental Psychiatry & Psychology, Department of Psychiatry, School of Clinical Sciences, Monash University, Melbourne, Australia
[4]Department of Obstetrics and Gynaecology, Monash Health, Melbourne, Australia
[5]Monash Maternity Services, Monash Health, Melbourne, Australia
[6]Centre of Perinatal Excellence, Melbourne, Australia

Corresponding Author:
Jacqueline Anne Boyle, PhD, MPH&TM, FRANZCOG, MBBS
Monash Centre for Health Research and Implementation
School of Public Health and Preventive Medicine
Monash University
43-51 Kanooka Gve, Clayton
Melbourne, 3168
Australia
Phone: 61 (613) 85722670
Fax: 61 (613) 9594755
Email: jacqueline.boyle@monash.edu

Abstract

Background: Identifying mental health disorders in migrant and refugee women during pregnancy provides an opportunity for interventions that may benefit women and their families. Evidence suggests that perinatal mental health disorders impact mother-infant attachment at critical times, which can affect child development. Postnatal depression resulting in suicide is one of the leading causes of maternal mortality postpartum. Routine screening of perinatal mental health is recommended to improve the identification of depression and anxiety and to facilitate early management. However, screening is poorly implemented into routine practice. This study is the first to investigate routine screening for perinatal mental health in a maternity setting designed for refugee women. This study will determine whether symptoms of depression and anxiety are more likely to be detected by the screening program compared with routine care and will evaluate the screening program's feasibility and acceptability to women and health care providers (HCPs).

Objective: The objectives of this study are (1) to assess if refugee women are more likely to screen risk-positive for depression and anxiety than nonrefugee women, using the Edinburgh Postnatal Depression Scale (EPDS); (2) to assess if screening in pregnancy using the EPDS enables better detection of symptoms of depression and anxiety in refugee women than current routine care; (3) to determine if a screening program for perinatal mental health in a maternity setting designed for refugee women is acceptable to women; and (4) to evaluate the feasibility and acceptability of the perinatal mental health screening program from the perspective of HCPs (including the barriers and enablers to implementation).

Methods: This study uses an internationally recommended screening measure, the EPDS, and a locally developed psychosocial questionnaire, both administered in early pregnancy and again in the third trimester. These measures have been translated into the most common languages used by the women attending the clinic and are administered via an electronic platform (iCOPE). This platform automatically calculates the EPDS score and generates reports for the HCP and woman. A total of 119 refugee women and 155 nonrefugee women have been recruited to evaluate the screening program's ability to detect depression and

anxiety symptoms and will be compared with 34 refugee women receiving routine care. A subsample of women will participate in a qualitative assessment of the screening program's acceptability and feasibility. Health service staff have been recruited to evaluate the integration of screening into maternity care.

Results: The recruitment is complete, and data collection and analysis are underway.

Conclusions: It is anticipated that screening will increase the identification and management of depression and anxiety symptoms in pregnancy. New information will be generated on how to implement such a program in feasible and acceptable ways that will improve health outcomes for refugee women.

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KEYWORDS

mental health; refugees; transients and migrants; pregnancy; prenatal care; mass screening

Introduction

Background

The perinatal period (from conception to 12 months following birth) is a time of increased vulnerability for the onset or recurrence of mental health disorders [1]. Perinatal depression and anxiety [2] affect up to 20% of all women and are recognized by the World Health Organization as major public health issues [3].

Perinatal mental health disorders have direct effects on women, their children, and families [4], including disrupted attachment between mother and infant [5] and elevated risk of maternal suicide. The latter is one of the leading causes of maternal death in high-income countries [6,7]. There is a substantial financial burden of maternal perinatal depression to individuals, private health insurance, governments, and the economy. For example, within the Australian economy, this was estimated at Aus $433.52 million in 2012 [8], and 8.1 billion pounds in the United Kingdom in 2014 [9]. Many factors contribute to a woman's risk of developing perinatal mental health disorders. These include a history of mental health disorders, low socioeconomic status, intimate partner violence, isolation, previous trauma, and stressful life events [4,7,10-12].

Routine, standardized screening in pregnancy for mental health disorders is recommended in high-income countries, including the United Kingdom [13], the United States [14], and Australia [1]. Implementation of such processes requires consideration of each setting [15]. In Australia, these recommendations have not been well implemented because of significant barriers at both the level of the service and the individual. This represents a critical gap, and a lost opportunity, with women and families bearing the impact of missed diagnosis, early management, and support. Addressing these barriers is key to improving health care for women at increased risk.

Refugee Women

The impact of the refugee experience on women cannot be underestimated. Women who are refugees have experienced one or more acts of violence related to war, persecution, gender-based violence, protracted situations of uncertainty for the future, and discrimination [7]. High rates of psychological disorders are evident and exacerbated by resettlement stressors such as language barriers, separation from or loss of family, cultural barriers, and marginalization [7,16,17]. The prevalence of mental health disorders in conflict-affected populations (men and women combined) is estimated to be 31% [18]. A recent systematic review of perinatal mental health of migrant women from low- and middle-income countries reported a pooled prevalence of 31% for any depressive disorder and 17% for a major depressive disorder [16]. Data specifically on mental health disorders in pregnancy for refugee women are lacking.

Screening may not be offered in routine care owing to a number of reasons: lack of validated screening tools in languages other than English; lack of interpreters; and lack of health professional skills and knowledge [1]. Previous research indicates that perinatal mental health screening is an acceptable practice in the maternity setting [19-21]. However, there is a paucity of published research focusing on women from culturally and linguistically diverse (CALD) backgrounds. To our knowledge, this is the first study that focuses on refugee women living in a resettlement and high-income country. Given the magnitude of the current global refugee crisis and migration patterns resulting in many CALD women living in high-income countries, our study will provide contemporary evidence on the acceptability and feasibility of perinatal mental health screening for this population.

Context

Australia's Multicultural Community

In 2016, Australia's population was 23.4 million, of whom approximately 6 million (26%) were born overseas. Nearly 1 in 5 (18%) migrants have arrived since 2012, and over 300 separately identified languages are spoken in Australian homes [22]. In 2015, 25% of women who birthed in Australia were born overseas [23]. People arrive in Australia through 2 main migration programs: the migrant program for skilled workers and family migrants or the humanitarian program for refugees and those in refugee-like situations [24]. In 2017-2018, Australia's total migration was 162,417, including 18,750 places allocated to the humanitarian stream [25,26].

Study Location

This study is being conducted in a large public health service in the southeast suburbs of Victoria's capital city, Melbourne, in which perinatal mental health screening is not yet routine. It is one of Australia's largest maternity providers and is located in a major area of refugee resettlement. The state of Victoria

has the highest settlement of refugees in Australia, receiving approximately 33% of the national intake [27]. In the past 10 years (2008-2018), over 11,000 people from a refugee background have resettled in the southeast suburbs of Melbourne, the highest resettlement catchment in Victoria for refugees [28]. In addition, there are over 7000 people seeking asylum, who arrived without a valid visa, currently living in Victoria, representing about 40% of the national total [29]. Demographic trends for people of a refugee background show that most are aged under 35 years and approximately 50% are females [28]. Furthermore, this region of Melbourne is the most culturally diverse community in Australia, with residents from 157 birth places [30,31] and 45% to 60% of women who birthed were born overseas. It is one of the most socially disadvantaged areas in Australia, meaning many people are on the lowest quintile for access to material and social resources [32]. As no mental health screening currently takes place in pregnancy at this health service, it is expected that the prevalence and burden of diagnoses of depression and anxiety disorders in refugee women will be underestimated. Given the current understanding of the prevalence of such disorders among pregnant women generally and the refugee population specifically, this suggests a major gap in pregnancy care.

Australia's Health Care System

Funded by the federal government, Medicare is Australia's health care system which provides universal access to public hospital care, primary health care, and some allied health services [33]. Hospital care is free for a public patient at a public hospital with other services free or at a reduced cost. Eligibility for Medicare includes Australian citizenship, permanent residency, or having applied for permanent residency. A permanent protection visa, for people from a refugee background, also confers access to Medicare. For those seeking asylum, a number of factors, including Medicare eligibility, can influence access to universal health care. Successive Victorian state governments (where this study is based) have shown a commitment to optimizing health outcomes for people of a refugee background by investing in initiatives such as the Victorian Refugee Health Program and Refugee Fellow Program [34]. Furthermore, the Victorian Department of Health's *Guide to asylum seeker access to health and community services in Victoria 2011*, supports access to health care in a state-funded facility, regardless of Medicare status [35].

Pilot Work Informing the Program

Significant stakeholder engagement and formative research identified barriers and enablers to implementing a perinatal mental health screening program. Stakeholder engagement was undertaken across the state and included refugee health services, academics, community and hospital health services, and mental health and maternity health services. Interviews with 28 health care providers (HCPs) and 9 community representatives from diverse ethnic backgrounds identified a number of needs such as staff training in mental health screening and safety planning for women at risk, robust referral pathways, and translated versions of the Edinburgh Postnatal Depression Scale (EPDS) [36]. Community representatives identified additional factors such as awareness of mental health, appropriateness of tools, and availability of interpreters [36]. Importantly, this research reported strong support from the community and HCPs to undertake screening, identify women at risk, and provide early support and assistance [36]. On the basis of this formative research and in collaboration with the maternity and refugee health services in Southeast Melbourne, community women, nongovernment organizations, and academics, the co-designed screening program with refugee-appropriate referral pathways commenced in 2016.

Screening Tools

The Edinburgh Postnatal Depression Scale

The EPDS is one of the most widely accepted screening measures for depression and anxiety symptoms in the perinatal period. It has been validated for use in pregnancy and the postpartum period [1] and has been validated in English as well as a number of other languages [37-39]. It is a 10-item, self-report questionnaire used to detect symptoms of emotional distress over the past 7 days [40]. The EPDS has been used internationally since its inception in 1987 and is available in many languages.

The English version of the EPDS performs with moderate sensitivity 0.83 (0.76-0.88) and high specificity 0.90 (0.88-0.92) in pregnancy [1]. The recommended cutoff score for use in general populations is 13 or above, indicating that depressive symptoms have been endorsed and signifying a high risk for probable depression which requires further clinical assessment. For women of CALD backgrounds, a lower cutoff score is recommended to balance psychometric performance with differences in cultural practices, beliefs, and degree of stigma [1]. Therefore, an EPDS cutoff score of ≥9 is used in this study, based on previous validations of EPDS translations with women of CALD backgrounds [41]. Although the EPDS was not designed to measure anxiety disorders, high scores on items 3, 4, and 5 have been found to be sensitive to symptoms of anxiety [42]. A score of ≥4 for the anxiety subscale is considered indicative of a high risk of anxiety symptoms and requires further assessment [42]. The final item (question 10) on the EPDS assesses the prevalence of suicidal ideation and risk of self-harm.

The Psychosocial Screening Tool

The Monash Health psychosocial needs assessment is a 23-item, locally developed, self-report measure specific to the health service that asks questions about risk factors for perinatal mental health disorders such as past birthing experiences causing stress or anxiety, social factors (such as housing and financial stress), experience of violence and safety at home, and a history of mental health disorders. In routine care, women complete the measure themselves or with the midwife at their booking visit. Respondents are required to provide "yes" or "no" answers and 4 nested text questions allow free-text responses.

For this study, the EPDS and the Monash Health psychosocial needs assessment have been translated to 7 refugee languages common in Southeast Melbourne: Arabic, Burmese, Dari, Farsi, Hazaragi, Pashto, and Tamil.

Research Questions

The primary research questions are as follows:

1. Are refugee women more likely to screen risk-positive for depression and anxiety on the EPDS than nonrefugee women?
2. Does screening in pregnancy using the EPDS enable better detection of symptoms of depression and anxiety in refugee women compared with current routine care?

Secondary Research Questions

We will also explore the following secondary questions:

1. Is perinatal mental health screening in pregnancy using an electronic platform acceptable and feasible to refugee women?
2. What are the barriers and enablers to the screening being perceived as a feasible and acceptable part of the routine practice by maternity HCPs?

Hypotheses

We hypothesize that a perinatal mental health screening program that addresses key concerns of women and HCPs can improve identification of symptoms of perinatal depression and anxiety in refugee women. We also hypothesize that co-designed screening can be implemented within a large and busy maternity service in a manner that is acceptable to both women and health service staff.

Methods

Setting

The study is being conducted at a refugee antenatal clinic (RAC) designed for refugee women in Southeast Melbourne, Australia. This clinic operates 1 day per week and is supported by a refugee health nurse liaison (RHNL) and 2 bicultural workers. On receipt of a general practitioner (GP) referral for maternity care, all women are allocated, by hospital clerical staff, to either the RAC or one of the other antenatal clinics on the basis of availability and preference. Therefore, refugee women also attend the other maternity clinics at the health service and nonrefugee women attend the RAC. On average, 13 women attend their first appointment with a midwife each week at the RAC. Approximately half of the women attending are from a refugee background or considered refugee-like, that is, arrived in Australia on a spousal visa from a refugee-source country, including Afghanistan, Myanmar, Iraq, the Republic of South Sudan, and Sri Lanka.

Procedures

Ethics Approval

This project has been approved by the Monash Health Human Research and Ethics Committee number 14475L.

Participants and Recruitment

The day before the first appointment, a female Afghan bicultural worker (RA) or one of the researchers (RB) telephones women to remind them of their appointment and to explain the screening and recruitment process for the research. Interpreters are used for women who do not speak the same language as RA or RB. Researchers are present at the clinic on the day of the appointment and obtain written informed consent from each participating woman. Consent is requested to access data from their medical health records at the hospital, GP records, and Monash Health Refugee Health and Wellbeing (RH&W) service records. This will enable evaluation of the screening results, referrals, and subsequent diagnosis and management. Women are also invited to participate in the acceptability phase of the project.

All staff working in the RAC (clerical staff, midwifery, medical, bicultural workers, and RHNL) and at the RH&W (psychologists and counselors) are invited to participate in the evaluation of the feasibility of the program.

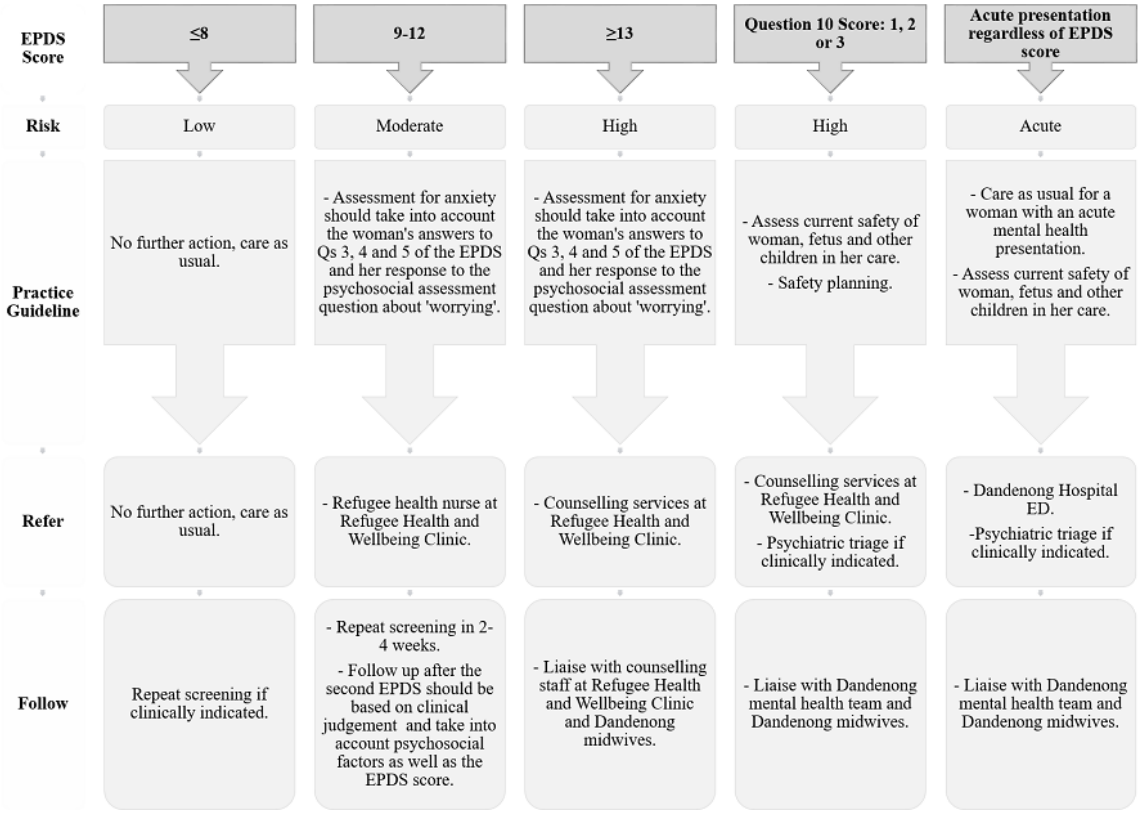
Intervention

On the day of the first appointment, all women attending the RAC are given an iPad to complete the screening (EPDS and Monash Health psychosocial needs assessment) using the digital platform iCOPE. iCOPE has been developed and piloted by the Centre of Perinatal Excellence (COPE, Australia) [43]. Women are able to complete the screening in their chosen language in the clinic waiting room and interpreters or bicultural workers are available to assist. Screening is repeated in the third trimester. It takes approximately 6 to 10 min for a woman to complete the screening on her own, or slightly longer if an interpreter is used. The iCOPE platform automatically calculates the overall EPDS score, the anxiety subscore (based on responses to question 3, 4, and 5), and highlights the response to question 10, which assesses risk of self-harm. Data are securely stored in compliance with industry regulations [43].

Co-Designed Referral Pathways for Refugee Women

During the appointment, the midwife discusses the result with the woman and initiates referral as appropriate. If the overall EPDS score is ≥9, the score for the anxiety subscale is ≥4, or the response to question 10 (self-harm) is positive, the RHNL is notified and further mental health and psychosocial assessment is undertaken. If the assessment by the RHNL indicates the woman is acutely ill, at risk of harming herself or others, an immediate referral to the hospital emergency department “and” or “or” psychiatric services is made. If the woman is not acutely unwell, the RHNL will refer to the RH&W counseling or to their GP, if preferred. If the result is between 9 to 12, a repeat screen in 2 to 4 weeks is recommended (see referral pathways, Figure 1). On completion of screening, women are provided a report in their chosen language that explains their results and a link to further resources and supports via email. A clinical report and management guide is also immediately generated for the midwifery appointment. If other factors are present, such as housing concerns or intimate partner violence, appropriate referrals are made as per usual care to services such as social work or legal services.

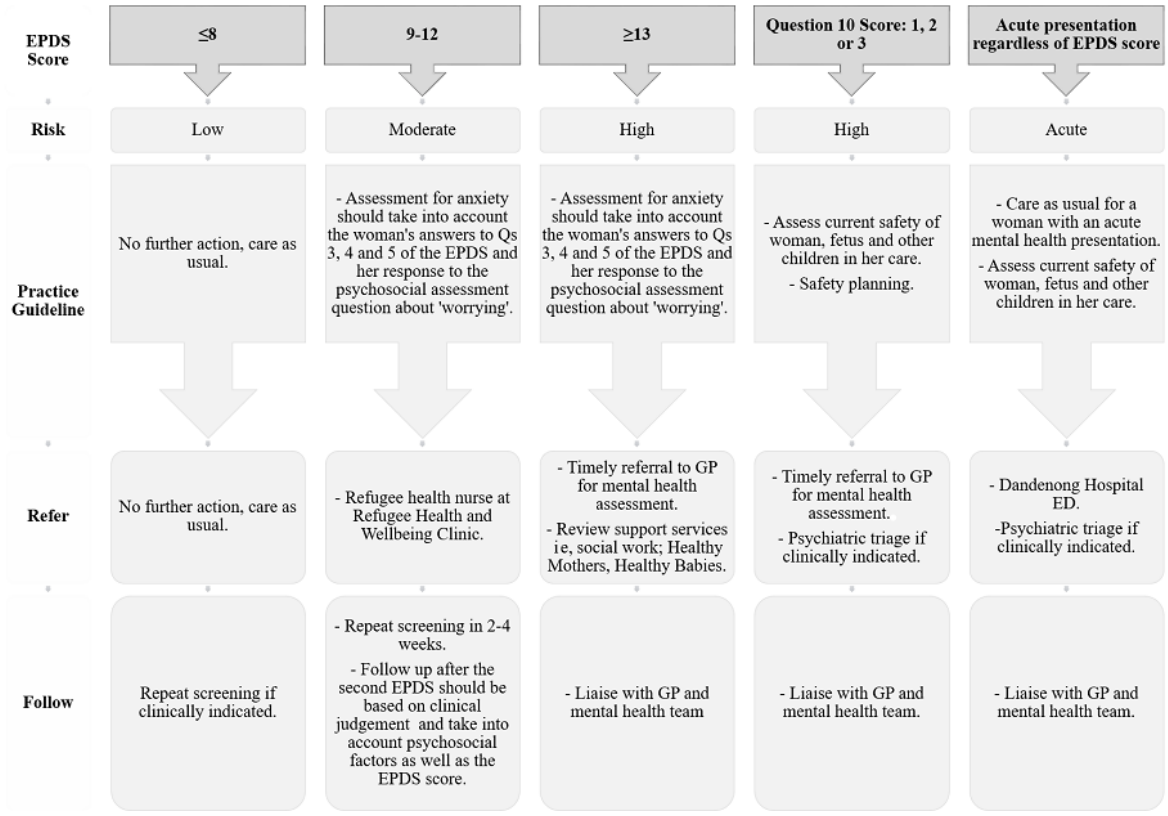
Figure 1. Referral pathway for women of refugee background. ED: emergency deparmtent; EPDS: Edinburgh Postnatal Depression Scale.



Comparison Group 1: Nonrefugee Women Attending the Refugee Antenatal Clinic

Nonrefugee women who attend the RAC also complete screening of the EPDS and the Monash Health psychosocial needs assessment using the iCOPE platform. Referral options include referral to the hospital emergency or psychiatric services if women are acutely unwell. For others, options include repeat screening in 2 weeks, allied health support such as social work, and referral to the woman's GP (see referral pathways for nonrefugee women, Figure 2).

Figure 2. Referral pathways for women of nonrefugee background. ED: emergency department; EPDS: Edinburgh Postnatal Depression Scale; GP: general practitioner.



Comparison Group 2: Refugee Women Attending Other Routine Antenatal Services at the Same Hospital

Refugee women also attend other antenatal clinics at the health service. Routine care at these clinics include completing a paper-based Monash Health psychosocial needs assessment (no EPDS) with the midwife during the first antenatal appointment. Routine referral pathways are not proscriptive but may include the RHNL, GPs, and services such as social work.

Evaluation of the Perinatal Mental Health Screening Program

Research Questions 1 and 2

Medical records will be audited for women attending the RAC and participating in the research program (119 refugee women and 155 nonrefugee women) and for a random sample of refugee women attending routine maternity clinics (non-RAC) during the study period (n=34). Information collected will include demographic data (including factors such as age, country of birth, time since arrival in Australia, marital status, number of pregnancies and births, and need for an interpreter), medical history (eg, diabetes, hypertension, and smoking), and psychosocial needs assessment results.

For those attending the RAC, the additional information of the screening report, EPDS scores (total, anxiety subscore, and Question 10 score) are recorded.

For the refugee women attending the non-RAC clinic, who do not participate in the screening program, any diagnosis of past or present mental health disorders and any relevant referral or management are recorded.

Data will be deidentified and entered into a REDCap database (Vanderbuilt, USA) [44] for collation and analysis. To address research question 1, the proportion of refugee women who screen positive on the EPDS for depression and anxiety will be compared with the proportion of nonrefugee women who screen positive.

To address research question 2, the proportion of refugee women who screen positive to depression or anxiety on the EPDS will be compared with the proportion of nonrefugee women attending routine maternity clinics who are identified with mental health disorders.

Research Question 3

To evaluate the women's acceptability of the screening program, women from the majority population groups at the RAC (refugee: Afghan and Burmese; nonrefugee: Indian and Vietnamese) are invited to participate in either a focus group or an interview to discuss their experiences of screening and referral. Interpreters will be engaged to maximize inclusion. Focus groups "and" or "or" interviews will continue until data saturation of themes is achieved.

Research Question 4

The Normalization Process Theory to Assess Health Care Providers' Views on Implementation:

All HCPs and clerical staff involved in the screening program (at the RAC and the RH&W) are invited to participate in an evaluation of implementation processes. This includes completion of the 23-item Normalization Measure And Development (NoMAD) online survey adapted for this study and participation in an interactive focus group or interview using

the Normalization Process Theory (NPT) toolkit. The NoMAD was distributed through Qualtrics (Provo, Utah, USA). The NPT toolkit has been selected and adapted for this project [45] as it focuses on implementation and assesses 4 relevant constructs: (1) coherence (how do staff make sense of the program when operationalizing the new set of practices), (2) cognitive participation (what work are the staff required to do to build and sustain a community of practice around the program), (3) collective action (what operational work is required by the staff to enact the new practice), and (4) reflexive monitoring (appraisal by the staff in understanding how this new set of practices affects them and others around them) [45].

Medical Records Audit

Women Attending the Refugee Antenatal Clinic

The medical records audit already described notes referrals to primary care, allied health, counseling, psychiatry, emergency services, or others, within and outside the hospital, and referrals made following screening with the EPDS and psychosocial needs assessment or in response to other clinical indications. The number of women who attend appointments arising from these referrals within the hospital or at the RH&W will be recorded. When a referral has been made to a GP (external to the health service), the GP practice is contacted to ascertain whether the woman attended for a formal assessment and diagnosis, the outcome, and any subsequent management plan.

Women Attending the Nonrefugee Antenatal Clinic

Similar data are collected about referrals made based on clinical assessment of need and subsequent attendance.

Outcome Measures

Primary Outcomes

The primary outcome is the proportion of women in 3 groups (refugee women screened, nonrefugee women screened, and refugee women receiving routine care) with symptoms of depression and/or anxiety.

Secondary Outcomes

Secondary outcomes include identification of factors that will influence broader implementation of screening:

- Factors that facilitate acceptability of the program to women
- Factors impacting positively and negatively on the feasibility of program implementation at a systems level.

Analysis Strategy (Sample Size Justification)

Research Question 1: Are Refugee Women More Likely to Screen Risk-Positive for Depression and Anxiety on the Edinburgh Postnatal Depression Scale Than Nonrefugee Women?

It is estimated that 40% of refugee women [16] and 20% of nonrefugee women will have an overall EPDS score of ≥9 [1]. The number of women required to detect a difference of 20% between the 2 groups, with 90% power, is 119 per group.

Additional analyses will assess differences in the proportion who score positive for anxiety or at-risk on question 10 of the EPDS.

Research Question 2: Does Screening in Pregnancy Using the Edinburgh Postnatal Depression Scale Enable Better Detection of Symptoms of Depression and Anxiety in Refugee Women Compared With Current Routine Care?

It is estimated that 40% of refugee women will have an overall EPDS score of ≥9 [7,16,46]. Current health service data indicate that less than 5% of women attending routine maternity care are recorded as having a mental health disorder. The number of women required to detect a difference of 20% between the 2 groups, with 80% power, is 34 per group.

Statistical Analysis for Research Questions 1 and 2

Data will be assessed using Stata Statistical Software: Release 14 (StataCorp, College Station, TX, US) [47] and will use chi-square tests for proportions, Student *t* test for comparisons of means, Wilcoxon rank sum tests for comparison of medians, and paired *t* test to compare the EPDS and anxiety subscores between initial and third trimester screening. Univariable and multivariable logistic regression analyses will be used to assess the impact of demographic factors such as marital status, country of birth, time since arrival in country, age, and parity on the primary outcome (overall EPDS score of ≥9).

Research Question 3: Is Perinatal Mental Health Screening in Pregnancy Using an Electronic Platform Acceptable and Feasible to Refugee Women?

Qualitative data will undergo thematic analysis to enable in-depth exploration of the data. Interviews will be audio recorded and transcribed verbatim. Transcripts will be read several times to obtain a sense of the whole before analysis. Overall, 2 researchers will independently conduct the initial narrative analysis using NVivo 11 (QSR International, Australia) qualitative data analysis software [48]. In the second phase, pieces of the data conveying the situation, the experiences, and the beliefs of participants will be identified and highlighted. A third phase involves the data being organized into patterns and emerging categories. Finally, a process of synthesis of the data will be undertaken that will result in the identification of major themes [49,50].

Research Question 4: What Are the Barriers and Enablers to the Screening Being Perceived as a Feasible and Acceptable Part of the Routine Practice by Maternity Health Care Providers?

A similar process will be undertaken with the NPT-based interview and focus group transcripts with the HCPs. Separate analysis of the NoMAD quantitative data (online survey) will be undertaken to assess responses and assess any differences by factors such as HCP type, age, and years of practice. The qualitative and quantitative data will then be combined, and mixed-methods analytic techniques will be applied [50]. Merging and connecting data and finally interpreting the data enables the researcher to draw inferences on the overall mixed-methods analysis [50].

Results

Recruitment of 119 refugee women and 155 nonrefugee women is complete. Data collection and analysis are underway. The cohort reflects the multicultural aspects of the community, with 248 of 274 (90.5%) women born overseas and 190 of 274 (69.3%) women arriving in Australia between 2008 and 2017.

Discussion

Stakeholder engagement and governance are key components of this research program. This ongoing stakeholder involvement has enabled the program to be co-designed and to evolve to meet stakeholder needs. The steering committee comprises staff from key hospital departments, GP liaison, RH&W, the nongovernment organization COPE, and academic experts in psychology, midwifery, obstetrics, and public health. This committee has met fortnightly for 2 years to plan, implement, and evaluate the program. The committee addresses concerns of the research team or hospital staff as they arise and responds with practical solutions. A community advisory group comprising women from 8 different countries also meets bimonthly and has been instrumental in planning the implementation and evaluation such as recruitment strategies, resources, and facilitating an understanding of the cultural complexity of the women participating.

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Authors' Contributions

The concept was initiated by JAB and MGH. The project plan has been jointly developed by all authors, and all authors have contributed to the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CALD: culturally and linguistically diverse
COPE: Centre of Perinatal Excellence
EPDS: Edinburgh Postnatal Depression Scale
GP: general practitioner
HCP: health care provider
NoMAD: Normalization Measure And Development
NPT: Normalization Process Theory
RAC: refugee antenatal clinic
RH&W: Monash Health Refugee Health and Wellbeing
RHNL: refugee health nurse liaison

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Protocol

Noncontact Heart and Respiratory Rate Monitoring of Preterm Infants Based on a Computer Vision System: Protocol for a Method Comparison Study

Kim Gibson[1], MAST; Ali Al-Naji[2], PhD; Julie-Anne Fleet[1], PhD; Mary Steen[1], PhD; Javaan Chahl[3], PhD; Jasmine Huynh[3], PhD; Scott Morris[4,5], MD, PhD

[1]School of Nursing and Midwifery, University of South Australia, Adelaide, Australia
[2]Electrical Engineering Technical College, Middle Technical University, Baghdad, Iraq
[3]School of Engineering, University of South Australia, Adelaide, Australia
[4]College of Medicine and Public Health, Flinders University, Adelaide, Australia
[5]Neonatal Unit, Flinders Medical Centre, Adelaide, Australia

Corresponding Author:
Kim Gibson, MAST
School of Nursing and Midwifery
University of South Australia
North Terrace
City East
Adelaide, 5000
Australia
Phone: 61 83022706
Fax: 61 83022168
Email: kim.gibson@unisa.edu.au

Abstract

Background: Biomedical research in the application of noncontact methods to measure heart rate (HR) and respiratory rate (RR) in the neonatal population has produced mixed results. This paper describes and discusses a protocol for conducting a method comparison study, which aims to determine the accuracy of a proposed noncontact computer vision system to detect HR and RR relative to the HR and RR obtained by 3-lead electrocardiogram (ECG) in preterm infants in the neonatal unit.

Objective: The aim of this preliminary study is to determine the accuracy of a proposed noncontact computer vision system to detect HR and RR relative to the HR and RR obtained by 3-lead ECG in preterm infants in the neonatal unit.

Methods: A single-center cross-sectional study was planned to be conducted in the neonatal unit at Flinders Medical Centre, South Australia, in May 2018. A total of 10 neonates and their ECG monitors will be filmed concurrently for 10 min using digital cameras. Advanced image processing techniques are to be applied later to determine their physiological data at 3 intervals. These data will then be compared with the ECG readings at the same points in time.

Results: Study enrolment began in May 2018. Results of this study were published in July 2019.

Conclusions: The study will analyze the data obtained by the noncontact system in comparison to data obtained by ECG, identify factors that may influence data extraction and accuracy when filming infants, and provide recommendations for how this noncontact system may be implemented into clinical applications.

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KEYWORDS

heart rate; respiratory rate; infant; electrocardiography; computers

Introduction

Background

The conventional method for monitoring vital signs of infants in the neonatal intensive care unit (NICU) is by the use of the electrocardiogram (ECG). This form of monitoring has disadvantages. One of the main concerns is that it is reliant on the use of electrodes that contain an adhesive layer [1]. The adhesive electrodes can cause damage to the fragile skin of preterm infants when removed and is the main source of skin breakdown in the NICU [2]. In addition, inaccurate apnea detection associated with artefact, generated by infant movement or cardiac activity, can influence monitoring accuracy [3].

Preservation of the integrity of the premature infant's skin is essential and certainly a challenge in the NICU [4]. The immature layers of the skin of premature infants predispose them to skin trauma, specifically, owing to a reduced number of fibrils that are spread sparingly, inhibiting the connection of the dermis to the epidermis. Owing to the weaker dermal-epidermal junction, the skin can be injured more easily, particularly because of adhesive removal [5]. Adhesive dressings and tapes used in the NICU may form a stronger bond with the epidermis in comparison with the dermal-epidermal junction; therefore, when adhesives are removed, the entire epidermis can be stripped. In response to limitations, manufacturers have developed alternative products such as hydrogel electrodes that do not contain an adhesive layer; however, they may not secure to the skin as effectively and thus are potentially problematic in terms of monitoring reliability [6].

An alternative technique to the use of ECG is noncontact photoplethysmography (PPGi). The PPGi principle is based on the concept that light is absorbed by blood more than by the surrounding tissue. A pulse will therefore produce small variations in the color of the skin, indicating that blood is being circulated owing to the redness of hemoglobin. Researchers have been able to extract the heart rate (HR) by filming and magnifying this variation in skin color changes [7,8]. HR can also be detected from filming and magnifying the head motion of a subject. The internal carotid arteries supply oxygenated blood to the brain and the external carotid arteries supply the neck and face. Owing to pressure changes when blood is pumped through these major blood vessels, the head will oscillate by approximately 5 mm in amplitude [9].

To capture the respiratory rate (RR), movement of the chest wall can be observed. The chest rises from movement of the diaphragm during inspiration, typically from 4 mm to 12 mm [10]. To ensure the signals captured from skin, head, and chest variances after magnification are enhanced and clear of background noise, an improved video magnification technique can be applied. These algorithms have been previously described [11,12]. The end-product is a graphic panel of the 2 sources of data extraction using skin color and motion magnification (from the head or thorax).

In our previous study [13], the technique of motion magnification was tested using healthy children from the ages of 1 to 5 years who were situated in different lighting conditions with or without a blanket covering them. Noncontact data were compared with a respiratory belt transducer and commercial sleep monitor. This yielded positive results with a cross-correlation coefficient of .9812, making it suitable for biomedical applications. This technique needs to be further studied to determine feasibility with a larger sample size and by varying factors common to the neonatal population.

Objective

The aim of this preliminary study is to determine the accuracy of a proposed noncontact computer vision system to detect HR and RR relative to the HR and RR obtained by 3-lead ECG in preterm infants in the neonatal unit. The specific objectives are as follows:

1. To determine if the noncontact system is accurate for measuring neonatal HR and RR when compared with ECG.
2. To identify factors that may influence data extraction and accuracy when filming preterm infants and provide recommendations for method improvement.
3. To provide an insight on how this noncontact system may be implemented for real-time and prototype development.

This technology may have the potential to replace conventional ECG and therefore avoid the adverse effects of its use with the preterm population.

Methods

Study Design

This is a single-center cross-sectional study of the proposed noncontact computer vision system based on quantitative methods. The concepts of PPGi and motion magnification will be applied to extract physiological data, with a statistical analysis of the results to quantify the relationship between the 2 methods of HR and RR monitoring using the Bland-Altman method [14].

System Framework and Data Analysis

This section describes the framework used to extract HR and RR based on the physiological variations caused by cardiopulmonary activity from 2 different regions.

To extract the cardiac signal, it is necessary to amplify the subtle color variations on the skin surface using the standard Eulerian Video Magnification (EVM) method [15]. However, some modifications have been applied to the EVM method to suit the proposed monitoring system and provide some improvements related to reducing the execution time and motion artefacts.

These modifications include using a wavelet pyramid decomposition and an elliptic band-pass filter instead of the Laplacian pyramid decomposition. After amplifying the video, the region of interest (ROI) will be manually localized using the MATLAB built-in function *ginput*. The brightness values of the pixels within the selected ROI will then be spatially averaged to obtain pulsatile amplitude traces obtained from Red, Green, Blue (RGB) channels, as shown in the following equation:

where *I (x,y,t)* is the brightness pixel value at image location *(x,y)* at time *(t)*, and |*ROI* | is the size of the selected ROI. As the G channel has the most apparent cardiac frequency band among other channels (R and B) [16-18], the $i_G(t)$ signal will be selected to estimate the cardiac signal. A spectrum analysis approach based on the Fast Fourier Transform (FFT) will then be applied on the $i_G(t)$ signal to transform it from the time domain to the frequency domain. The frequency band of interest (0.5-3 Hz) that corresponds to 30 to 180 bpm will then be selected using a separating ideal band-pass filter, followed by the inverse FFT to transform the filtered cardiac signal from the frequency domain to the time domain. Finally, peak detection based on the MATLAB built-in function, *findpeaks*, will be used to calculate the number of peaks of the acquired signal.

The variations in thoracoabdominal wall movement during respiration reflect directly in the spatial changes of intensity values in the video recording. The motion magnification approach proposed in previous work [11] will be first utilized to amplify the recorded video before data analysis. As the camera will capture the video in the RGB color space and to separate the intensity information from the color information, the RGB color space is converted to the YIQ color space using MATLAB's built-in function called *rgb2ntsc*. The thoracoabdominal region will be manually localized where the cardiopulmonary signal is most pronounced using the MATLAB built-in function, *ginput*. The next processing step is to average the intensity pixel values over the frame sequences of the selected ROI from the Y channel of the YIQ color space, as shown in the following equation:

where *I (x,y,t)* is the intensity pixel value at image location *(x,y)* at time *(t)*, and |*ROI* | is the size of the selected ROI. A spectral analysis method using FFT is then applied to transform $i_G(t)$ from the time domain to the frequency domain, followed by applying a separating ideal band-pass filter with selected frequencies of 0.15 to 2 Hz, corresponding to 9 to 120 breaths/min. The inverse FFT is then applied to transform the filtered breathing signal from the frequency domain to the time domain. Finally, peak detection based on the MATLAB built-in function, *findpeaks*, is carried out to identify the number of peaks of the acquired signal.

The measured value (M_v) of the HR and RR per minute can be calculated using the following equations:

The period (p) between 2 peaks (average) is:

where p is the number of peaks of the acquired signal and t is the length of the video signal in seconds.

The end-product is a graphic panel of the 2 sources of data extraction using skin color and motion magnification. As shown in Figure 1, HR and RR are clearly presented in accordance to the selected timeframe.

Participants

Participants will be selected using a convenience method. To assess the accuracy of the computer vision system in different situations, recruiting participants with confounding variables is necessary, such as respiratory support covering the face, variations in melanin concentration of infant skin, being cuddled by their parent, being positioned in an incubator, or receiving phototherapy producing a blue-light source. The inclusion criteria are as follows: infants below 37 weeks of corrected gestation who are monitored using the unit's regular ECG monitor during the time of data collection to be used as a reference to validate accuracy of the proposed system. The exclusion criteria are as follows: term infants (≥37 weeks of gestation) or preterm infants that are not on ECG monitoring, who are likely to be discharged at the time of data collection, or who have major congenital abnormalities that could possibly make them identifiable in publications. Informed written consent will be obtained. Ethical approval for this study was obtained from the Southern Adelaide Local Network Research Committee (HREC/17/SAC/340; SSA/17/SAC/341) and the University of South Australia Human Research Ethics Committee (protocol number 0000034901).

Sample Size

A sample size of 10 participants will provide 2 data points per participant (from PPGi and motion magnification), totaling 20 data points. This targeted sample size was determined given that this is a preliminary study investigating this novel technology still in its developmental phase. Results from this study will inform the rationale for conducting future large-scale studies.

Figure 1. MATLAB graphic panel of the proposed system. HR: heart rate; RR: respiratory rate.

Figure 6. Calculation 1.

$$i_R(t), i_G(t), i_B(t) = \frac{\sum_{x,y \in ROI} I(x, y, t)}{|ROI|}$$

Figure 7. Calculation 2.

$$i_Y(t) = \frac{\sum_{x,y \in ROI} I(x, y, t)}{|ROI|}$$

Figure 8. Equation 3.

$$\text{Time (seconds)} = \frac{\textit{number of frames}}{\textit{frame rate}}$$

Figure 9. Equation 4.

$$M_v = \frac{\textit{number of peaks}}{\textit{time}} = p \times 60 \text{ bpm}$$

Data Collection

Data collection will only commence after parents or guardians have acknowledged and signed the consent form provided. Participants will be filmed for approximately 10 min, which will provide adequate opportunity for data collection and variation in HR and RR. A Nikon D5300 and Nikon D610 camera will be used to film the infants and the cardiorespiratory monitor. Each camera will be mounted to a tripod and directed from approximately one meter away (Figure 2). The infant will not need to be repositioned for the purposes of the study as any sleeping position is acceptable. The researcher will ensure the ECG electrodes used for validation are correctly attached before filming. The entire body of the infant will be in the camera frame, with or without clothes or blankets, ensuring both methods of data extraction are possible. The infant will be filmed from various angles (eg, front on, from the back, and from the side) to assess accuracy from different perspectives.

Filming will take place by each camera concurrently, with the data and time of recording and participant number being noted. Clinicians will be able to have full access to the infant if required. If the infant was to have an apneic or bradycardic episode during filming, the clinician will be alerted by the unit's ECG monitor. Filming will continue during this event unless directed otherwise by either the clinician or parent or guardian, because capturing significant variations in HR and RR will strengthen the efficacy of the noncontact system.

Data Analysis

Phase 1

The first component of data analysis is data extraction using the noncontact system. The MATLAB environment—R2016a (MathWorks) with a Microsoft Windows 10 operating system will be utilized to conduct data analysis, producing the graphic panel for each participant (Figure 2).

Data points from both sources will be obtained at 3, 6, and 9 min for both RR and HR. A total of 3 data points will be determined as Altman and Bland [14] recommend that 2 or more measurements per participant be collected. The repeated measurements obtained from each participant will be averaged, which will not influence the bias between both measurements [19].

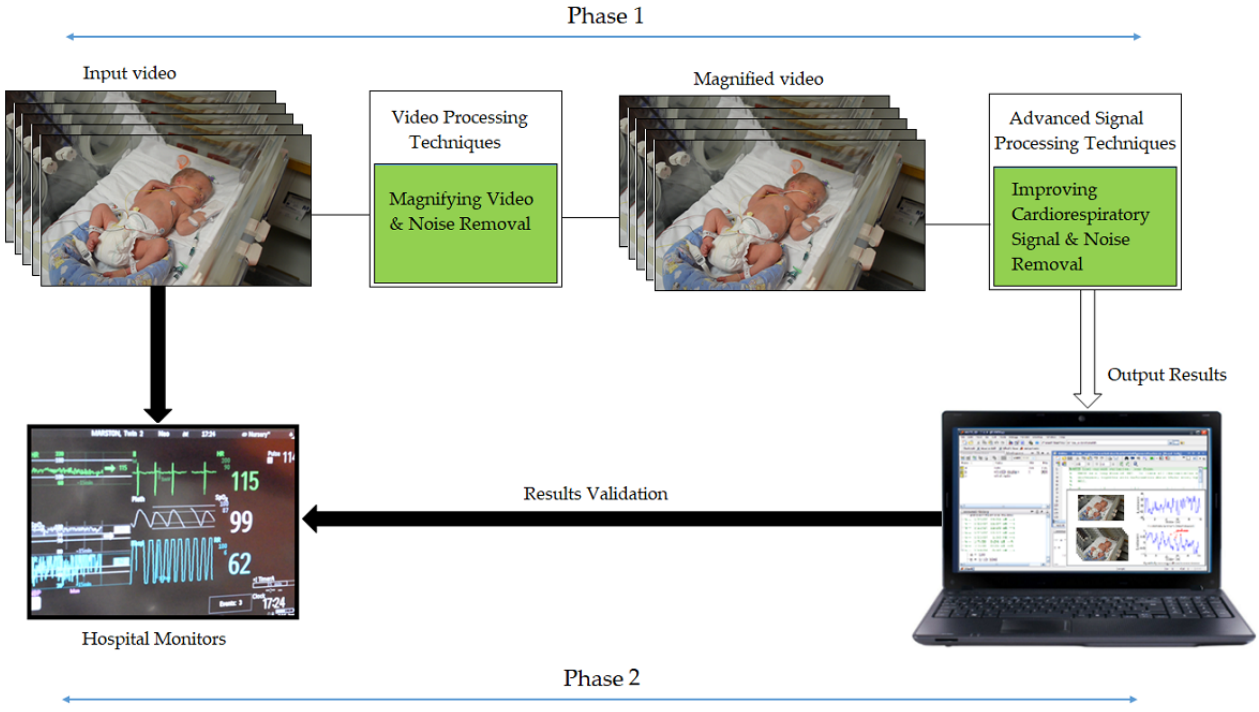
Owing to the potential for rapid fluctuations in infant HR and RR, the average HR and RR measurements over a 5-second period will be analyzed using the calculation previously described. The Phillips IntelliVue monitor that will be used to validate our results determines the HR by averaging the 12 most recent HR intervals from the ECG, and the RR is calculated by averaging the last 8 detected breaths [20].

Phase 2

The second component of data analysis is the statistical comparison of the 2 different methods. MedCalc Statistical Software version 18.2.1 [21] will be utilized to conduct this phase (Figure 3).

Figure 2. The experimental set-up for data collection.

Figure 3. Data analysis flowchart.



Clustered Regression Analysis

First, owing to collecting more than one measurement per participant, we cannot use a formal paired *t* test to test for zero bias between both methods. Therefore, clustered regression will be used to test the null hypothesis where the bias is zero.

Bland-Altman Analysis

Researcher KG will confirm the ECG readings at the selected intervals and compare the data extracted using the computer vision system which will be performed by researcher AA, limiting potential bias. A Bland-Altman analysis with multiple measurements per subject will be utilized from each method of data extraction (PPGi and motion magnification).

In total, 2 scatter plots (HR and RR) will be automatically formulated encompassing data for all participants using MedCalc software. The difference between the methods (input video vs ECG monitor; i, $d_i=y_{i2}-y_{i1}$) will be plotted against the average ($a_i=(y_{i1}+y_{i2})/2$) in the scatter plot [20 Stevens]. The formulation of this plot enables conclusions to be made with regard to whether the differences between the measurements are related to averages and to assess disagreement from possible error [14]. The scatter plot will be reviewed for possible errors such as

proportional error. The mean bias between the two methods and the 95% limits of agreement as the mean difference (1.96 SD) are calculated [19]. Once determined, the mean bias will be compared with the clinically acceptable difference (CAD). The a priori criterion for bias and the CAD will be defined as an interval around zero ($-c$,c) [22]. Therefore the CAD should be close to zero for deeming the 2 methods as interchangeable.

Results

Study enrolment and data collection began in May 2018. Results of this study have recently been published [23].

Discussion

Contribution to the Literature

We will be studying a real-life population in an environment that is characterized by variables demonstrated by other researchers to cause monitoring inaccuracy. Reduced environmental levels common in the NICU have been one of the main methodological challenges owing to impacting the PPGi signal to noise ratio with unwanted interference in related work [24]. Infants being covered by equipment or blankets have also been demonstrated to influence monitoring accuracy owing to difficulties in selecting an optimal ROI [1]. We have previously demonstrated accuracy with our algorithm to measure pediatric RRs in an environment with reduced lighting and with blanket coverings [13]. Therefore, our method may be able to address common accuracy issues with noncontact monitoring in the NICU.

Limitations

A possible threat to our method's internal validity is that the preexisting impedance monitoring will be utilized as the reference standard to validate data. Impedance monitoring can be influenced by patient movement or cardiac activity, thus impacting the RR signal [3]. Using the conventional ECG monitor to validate our results will be necessary to minimize disruption to participants for the sole purposes of this study. The application of additional modes for RR monitoring regarded as more accurate such as chest impedance belts or airflow detection methods will be considered for future large-scale studies [25].

The results will address the aim and objectives of this study and inform the design of future large-scale primary studies to refine methods, identify and address potential limitations of the technology, and evaluate the overall feasibility of the proposed noncontact system.

Authors' Contributions

All authors provided input for the development, design, and planning of the study. KG has led the conceptualization of this study and developed this protocol under the supervision of JC, JF, and MS. JC is the Principal Supervisor of this study. JH was responsible for developing the ethical clearance documents. SM provided site support and input into planning of the study. All authors contributed, edited, and reviewed the final version.

Conflicts of Interest

The primary researcher has no conflicts of interest to declare. Other members of the research team (AA and JC) may have input into the potential commercialization of the prototype. As such, the team will adhere to the principles of the Australian Code for the Responsible Conduct of Research [26].

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Abbreviations

CAD: clinically acceptable difference
ECG: electrocardiogram
EVM: Eulerian Video Magnification
FFT: Fast Fourier Transform
HR: heart rate
NICU: neonatal intensive care unit
PPGi: photoplethysmography
RGB: Red, Green, Blue
ROI: region of interest
RR: respiratory rate

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Corrigenda and Addenda

Title Correction: Clinical Outcomes of Pneumonia and Other Comorbidities in Children Aged 2-59 Months in Lilongwe, Malawi: Protocol for the Prospective Observational Study "Innovative Treatments in Pneumonia"

Amy Sarah Ginsburg[1], MPH, MD; Susanne May[2], PhD; Evangelyn Nkwopara[1], MS; Gwen Ambler[3], MPH; Eric D McCollum[4], MD; Tisungane Mvalo[5], MBBS, MMED, FC; Ajib Phiri[6], MD; Norman Lufesi[7], MPhil

[1]Save the Children, Fairfield, CT, United States

[2]Department of Biostatistics, University of Washington, Seattle, WA, United States

[3]PATH, Seattle, WA, United States

[4]Eudowood Division of Pediatric Respiratory Sciences, John Hopkins School of Medicine, Baltimore, MD, United States

[5]University of North Carolina Project: Lilongwe, Central Region, Lilongwe, Malawi

[6]Department of Paediatrics and Child Health, College of Medicine, University of Malawi, Blantyre, Malawi

[7]Ministry of Health, Republic of Malawi, Lilongwe, Malawi

Corresponding Author:
Amy Sarah Ginsburg, MPH, MD
Save the Children
501 Kings Highway E #400
Fairfield, CT,
United States
Phone: 1 206 258 1827
Email: aginsburg@savechildren.org

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The title of this paper (JMIR Res Protoc 2019;8(7):e13377) has been changed from:

> *"Clinical Outcomes of Pneumonia and Other Comorbidities in Children Aged 2-59 Months in Lilongwe, Malawi: Protocol for the Prospective Observational Study "Innovative Treatments for Pneumonia"*

to:

> *Clinical Outcomes of Pneumonia and Other Comorbidities in Children Aged 2-59 Months in Lilongwe, Malawi: Protocol for the Prospective Observational Study "Innovative Treatments in Pneumonia"*

The correction will appear in the online version of the paper on the JMIR website on August 26, 2019, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article also has been resubmitted to those repositories.

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Protocol

Text-Messaging, Online Peer Support Group, and Coaching Strategies to Optimize the HIV Prevention Continuum for Youth: Protocol for a Randomized Controlled Trial

Dallas Swendeman[1], PhD, MPH; Elizabeth Mayfield Arnold[2], MSW, PhD; Danielle Harris[1], MPH, MA; Jasmine Fournier[3], MS; W Scott Comulada[1], Dr PH; Cathy Reback[1], PhD; Maryann Koussa[1], MPH; Manuel Ocasio[3], PhD; Sung-Jae Lee[1], PhD; Leslie Kozina[3], RN, CCRC; Maria Isabel Fernández[4], PhD; Mary Jane Rotheram[1], PhD; Adolescent Medicine Trials Network (ATN) CARES Team[1,2,3,4]

[1]University of California, Los Angeles, Department of Psychiatry & Biobehavioral Sciences, Los Angeles, CA, United States

[2]Department of Family and Community Medicine, UT Southwestern Medical Center, Dallas, TX, United States

[3]Tulane University School of Medicine, Department of Pediatrics, New Orleans, LA, United States

[4]Nova Southeastern University, College of Osteopathic Medicine, Fort Lauderdale, FL, United States

Corresponding Author:
Dallas Swendeman, PhD, MPH
University of California, Los Angeles
Department of Psychiatry & Biobehavioral Sciences
10920 Wilshire Blvd, Suite 350
Los Angeles, CA, 90024
United States
Phone: 1 3107948128
Email: dswendeman@mednet.ucla.edu

Abstract

Background: America's increasing HIV epidemic among youth suggests the need to identify novel strategies to leverage services and settings where youth at high risk (YAHR) for HIV can be engaged in prevention. Scalable, efficacious, and cost-effective strategies are needed, which support youth during developmental transitions when risks arise. Evidence-based behavioral interventions (EBIs) have typically relied on time-limited, scripted, and manualized protocols that were often delivered with low fidelity and lacked evidence for effectiveness.

Objective: This study aims to examine efficacy, implementation, and cost-effectiveness of easily mountable and adaptable, technology-based behavioral interventions in the context of an enhanced standard of care and study assessments that implement the guidelines of Centers for Disease Control and Prevention (CDC) for routine, repeat HIV, and sexually transmitted infection (STI) testing for high-risk youth.

Methods: Youth aged between 12 and 24 years (n=1500) are being recruited from community-based organizations and clinics serving gay, bisexual, and transgender youth, homeless youth, and postincarcerated youth, with eligibility algorithms weighting African American and Latino youth to reflect disparities in HIV incidence. At baseline and 4-month intervals over 24 months (12 months for lower-risk youth), interviewers monitor uptake of HIV prevention continuum steps (linkage to health care, use of pre- or postexposure prophylaxis, condoms, and prevention services) and secondary outcomes of substance use, mental health, and housing security. Assessments include rapid diagnostic tests for HIV, STIs, drugs, and alcohol. The study is powered to detect modest intervention effects among gay or bisexual male and transgender youth with 70% retention. Youth are randomized to 4 conditions: (1) enhanced standard of care of automated text-messaging and monitoring (AMM) and repeat HIV/STI testing assessment procedures (n=690); (2) online group peer support via private social media plus AMM (n=270); (3) coaching that is strengths-based, youth-centered, unscripted, based on common practice elements of EBI, available over 24 months, and delivered by near-peer paraprofessionals via text, phone, and in-person, plus AMM (n=270); and (4) online group peer support plus coaching and AMM (n=270).

Results: The project was funded in September 2016 and enrollment began in May 2017. Enrollment will be completed between June and August 2019. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Conclusions: This hybrid implementation-effectiveness study examines alternative models for implementing the CDC guidelines for routine HIV/STI testing for YAHR of acquiring HIV and for delivering evidence-based behavioral intervention content in modular elements instead of scripted manuals and available over 24 months of follow-up, while also monitoring implementation, costs, and effectiveness. The greatest impacts are expected for coaching, whereas online group peer support is expected to have lower impact but may be more cost-effective.

Trial Registration: ClinicalTrials.gov NCT03134833; https://clinicaltrials.gov/ct2/show/NCT03134833 (Archived by WebCite at http://www.webcitation.org/76el0Viw9)

International Registered Report Identifier (IRRID): DERR1-10.2196/11165

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KEYWORDS

adolescents; HIV/AIDS; mHealth; homelessness; MSM; transgender; prevention

Introduction

Background

America's HIV epidemic among youth aged 12 to 24 years has significantly increased in the last 15 years [1,2]. Young people now represent 26% of the HIV epidemic [1,2] despite investments in evidence-based behavioral interventions (EBI) and more recent scale-up of innovative antiretroviral treatments that can stop acquisition of HIV, which are known as preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) [3,4]. Adolescents continue to become infected at disproportional rates [4]. It is critical to intervene with youth at high risk (YAHR) of acquiring HIV before they become infected. This study aims to intervene with YAHR with a set of interventions, which could be easily mounted, tailored, adapted over time, and broadly disseminated.

YAHR are those in urban epicenters and increasingly in the southeastern United States, particularly men who have sex with men (MSM) and transgender youth [1]. Homeless youth are also at elevated HIV risk, yet the last HIV seroprevalence study was conducted in 1991, showing 5.3% prevalence [5]. Youth in the criminal justice system may also be at elevated HIV risk [6,7]. YAHR are difficult to identify and intervene with in medical clinics because most youth (about 60% of general adolescent population) do not access health care [8-10]. Adolescents typically fail to disclose their sexual behaviors to their families or their physicians, most often because they are never asked about risk [11-13]. YAHR are likely to be encountered at agencies serving lesbian, gay, bisexual, transgender, and queer (LGBTQ) youth; homeless shelters; in the criminal justice system; and through in-person or Web spaces associated with sexual networking [14]. In each geographic epicenter of HIV, African American and Latino youth are at the highest relative risk of contracting HIV [1,15]. YAHR also typically seek peers, economic opportunities, and social services in the neighborhoods associated with the highest prevalence of HIV such as Hollywood in Los Angeles and the French Quarter in New Orleans [16]. This study uses community-based recruitment and screening to identify YAHR (see details in Rotheram-Borus et al [17]).

The current paradigm for reaching global HIV prevention goals (ie, increased uptake of the HIV prevention continuum [18]) is far more complex today than it was in the first 25 years of the epidemic. The US Centers for Disease Control and Prevention (CDC) recommends repeat and routine testing for HIV and sexually transmitted infection (STI) for YAHR every 3 or 6 months, as well as concurrently linking youth to HIV prevention and health care services and retaining them in care over time [19]. This study aims to operationalize and evaluate the impact of these guidelines using community-based recruitment and implementation of rapid diagnostic testing, referral and linkage to services, and easily scalable and tailorable technology-mediated interventions. The possibility now exists to implement biomedical and combination biobehavioral prevention for YAHR, which requires that youth know their serostatus (ie, be repeatedly tested for HIV over time), be linked to medical care, and consistently adhere to a strategy to protect themselves from HIV (eg, high adherence to PrEP, PEP, and condom use [18]). Textbox 1 summarizes the multiple endpoints for operationalizing uptake of HIV prevention continuum. These are particularly challenging tasks because the developmental challenges of youth evolve with age and may be more difficult for gay, bisexual, and transgender youth; homeless youth; and youth involved in criminal justice because of discrimination and stigma, which are often exacerbated for African American and Latino youth [11,20-23].

Textbox 1. The HIV prevention continuum for seronegative high-risk youth.

- Test negative for HIV
- Receive health care twice annually
- Adherence consistently to prevention options
  - Preexposure prophylaxis or
  - Postexposure prophylaxis after condomless sexual encounters or
  - Condom use
- Repeat HIV and sexually transmitted infection testing 3 times annually

A New Model for Intervention Design and Delivery

Traditional EBIs for HIV prevention rely on highly scripted and manualized protocols, delivered in-person, and that are time limited and became increasingly brief in numbers of and durations of sessions over the past 20 years [24]. Although EBIs for youth HIV prevention have been selected and diffused by the CDC on the basis of demonstrated efficacy in trials, they have been challenging to scale up and lack evidence for effectiveness [24]. These EBIs are highly structured and scripted manual-based protocols, which have been noted as being difficult to implement with fidelity and are not tailorable to intervention facilitators' and youths' varying styles, preferences, hierarchies of needs, development stages, and HIV risks. They also typically rely on in-person visits at community-based organizations (CBOs) or health care settings. Disruptive innovations of massively scalable mobile and social media technologies may be able to implement and broadly reach youth with prevention messages and linkage to services [24-26]. Bower and Christensen [27] defined the concept of disruptive innovations in *Harvard Business Review* as simpler, cheaper, and *good enough* solutions to meet the majority of consumers' needs and preferences relative to incumbent products and services that are often designed for the highest-need consumers, for example, ATM machines versus bank tellers, US $2 reading glasses versus specialized prescriptions, or minute clinics in pharmacies. Rotheram et al (2012) applied this concept to EBIs for youth behavioral and mental health problems by positing that interventions based on common practice elements identified across manualized EBIs, and technology-mediated modalities could be disruptive innovations that might be more scalable, adaptable, and amenable to providers' and patients' needs and preferences [24].

Advances in mobile phone and social media technologies have created opportunities to engage and intervene with large numbers of youth at relatively low costs, using technologies that permeate their daily routines [25,28]. This study will use 2 primary technology platforms, that is, text messaging and social media, in addition to telephone and in-person visits based on youths' preferences. Text messaging, email, and social media use are nearly universal among youth [29-31]. Approximately 90% of youth report having a mobile phone [31-33], 90% of them text about 30 times each day [31]; rates are similar for homeless youth but with some inconsistency in maintaining service [29,30,34]. Similarly, over 90% of youth access the Web daily, and smartphones have become the primary mode of accessing the internet for the majority of youth [31].

This study's automated and interpersonally delivered technology-mediated interventions are based on the shared features of existing EBI—we do not aim to create a new smartphone app or an EBI with a manual to be *replicated with fidelity* [35,36]. In the last 25 years, over 100 HIV EBIs and 36 adolescent sexual health EBIs have been identified by the CDC and other review bodies as efficacious [37-39] and supported for diffusion. Members of this study team rated the manuals of 5 of the CDC's most popular, behaviorally oriented primary prevention EBIs for adolescents [36,40,41,42], finding that each of them incorporated common processes, principles, and factors. Each of the EBIs are also based on cognitive behavioral theories, even though some researchers cited a more specific iteration (eg, social cognitive theory, theory of reasoned action, and the AIDS risk reduction model) or meta-theory (eg, information-motivation-behavior and social action theory). The EBIs had much more in common than different [36,40-42]. The intervention approach for this study is to focus on the common elements that many different interventions share, delivered by the most cost-efficient, scalable, and adaptable delivery strategies that permeate youths' daily routines: mobile and social media technologies.

This hybrid implementation-effectiveness study examines alternative models for implementing the CDC's guidelines for routine HIV/STI testing for YAHR of acquiring HIV and for delivering EBIs in modular elements instead of scripted manuals, while also monitoring implementation, costs, and effectiveness [43]. A randomized controlled trial (RCT) evaluates the efficacy and cost-effectiveness of the 4 intervention strategies of variable intensities and costs. This study aims to inform future prevention programs implemented by communities to avert the acquisition of HIV among young people by monitoring outcomes at 4-month intervals over 24 months.

Methods

Overview

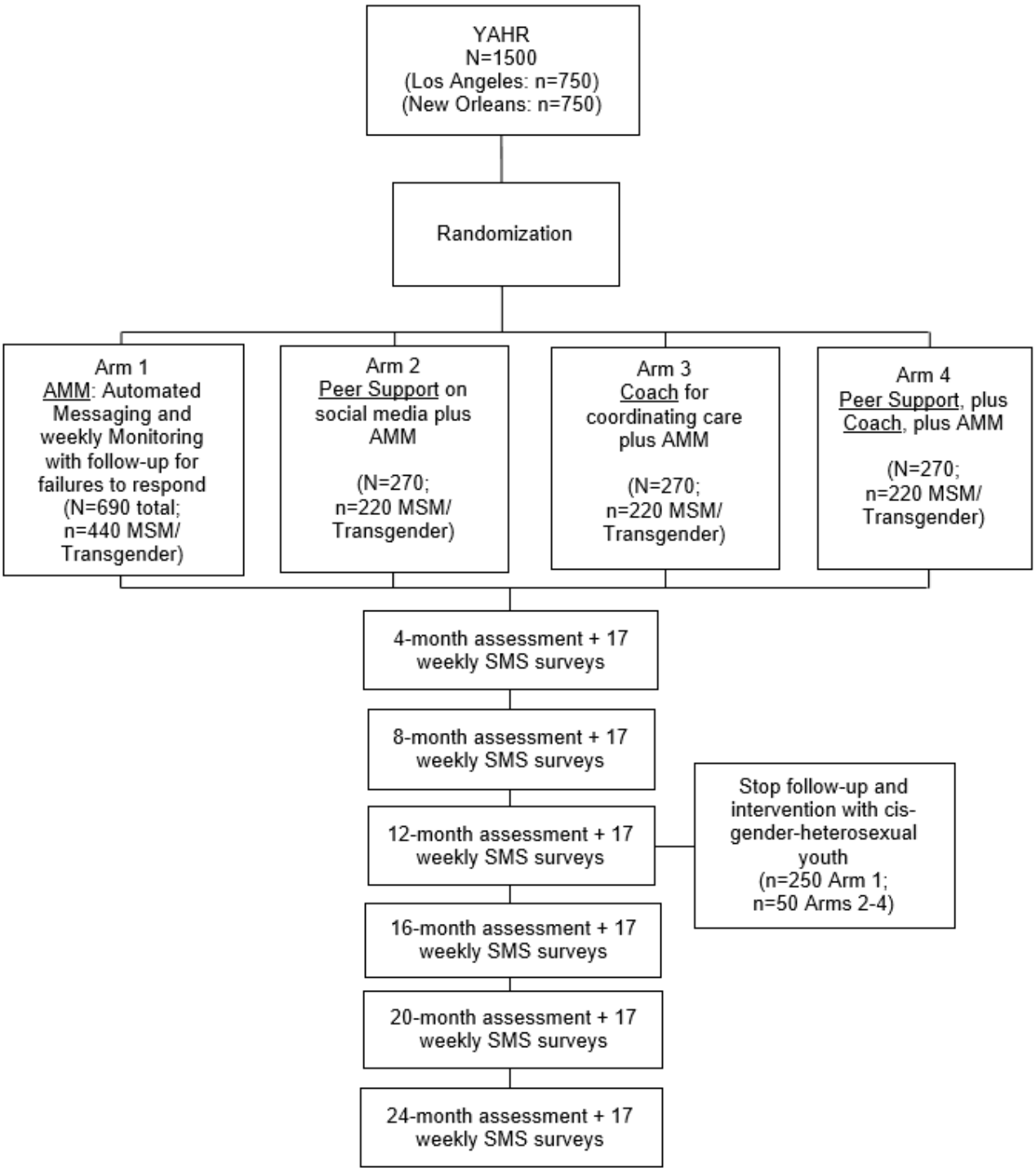
All procedures in this study have been approved by the institutional review board (IRB) of the University of California, Los Angeles, which serves as the single IRB of Record for researchers at collaborating institutions. This is 1 of 3 studies in a National Institute of Child Health and Human Development (NICHD)-funded U19 Cooperative Agreement for the

Adolescent (HIV Medicine) Trials Network (ATN) as well as a Management Core and Analytic Core [17,44-47]. This study began recruitment in May 2017. From June 2018 to December 2018, the protocol underwent a process of review and revision in collaboration with NICHD project scientists, the study's scientific monitoring committee, and an external statistical expert, to meet budget constraints and align more closely with ATN scientific priorities. The major changes were (1) to reduce STI testing frequency from every 4 months routinely to only at baseline, 12, and 24 months and rectal testing only (unless requested by youth or indicated by symptoms); (2) stopping follow-up and intervention at 12 months with youth who are not MSM or transgender; and (3) changing randomization allocations for person-mediated intervention arms to have statistical power for MSM and transgender participants with 70% retention rates.

Design

Figure 1 shows the study design overview. The randomized controlled factorial design assesses efficacy of 3 intervention strategies (arms 1-3) and their combination (arm 4). The person-mediated interventions in arms 2 to 4 have a sample size of 270 per arm with 220 MSM and transgender youth, whereas the larger sample of 690 in the automated intervention only (arm 1) is because of the broader U19 Cooperative Agreement's goal to identify youth acquiring HIV infection during follow-up to refer to a sister protocol on acute HIV infection [45], and earlier expectations to recruit youth that could be referred to other ATN protocols. Participants are followed longitudinally over 24 months (12 months for youth who are not MSM or transgender) and assessed at 4-month intervals by interviewers. Participants also complete a brief 7-question survey every week by text message (or email when nonresponsive to text messages). The overviews of assessments are provided below and described in detail in linked publications for the U19 [17,44-47].

Figure 1. Design of the randomized controlled trial for youth at high risk (YAHR) for acquiring HIV (n=1500). AMM: automated text-messaging and monitoring; MSM: men who have sex with men; SMS: short messaging service.



Recruitment

In both Los Angeles and New Orleans, the Recruitment, Engagement, and Retention Centers in the Management Core [17] are responsible for recruiting, enrolling, and following up with youth. Youth are primarily recruited from CBOs and clinics serving gay, bisexual, and transgender youth; homeless youth; and youth on probation or released from incarceration. Youth are also recruited through dating apps (eg, Grindr, Jack'd, and Scruff), including while present in social venues (eg, bars, clubs, and community events). We anticipate the study sample to be predominantly MSM and transgender, African American and Latino, and aged between 18 and 24 years. Youth are approached with verbal assent to complete brief screener questions and a rapid HIV test; however, youth aged between 12 and 14 years are asked to provide written voluntary informed consent to screen because of IRB requirements. Details on recruitment and screening are provided in other publications from the U19 [17,47] and briefly summarized below.

Eligibility

To screen as eligible for enrollment, youth must test seronegative on a rapid HIV testing at screening and report at least 3 of the following criteria: self-reporting as gay, bisexual, or transgender; African American or Latino race/ethnicity; having unprotected anal sex, sharing needles for injecting drugs, or an HIV-positive partner in the last 12 months; having been homeless (defined as not having a regular place to sleep for 3 or more months); illicit substance use (not including marijuana) in the last 12 months; having been hospitalized for a mental health disorder; having been in jail or on probation; having an STI in the last 12 months. Transgender and MSM youth are always eligible. Eligible participants are invited to enroll in the study with written informed consent.

Assessments

Following enrollment, participants complete a baseline assessment, which includes a questionnaire and a series of rapid diagnostic tests. These assessments are repeated at follow-ups. Participants receive a US $50 cash incentive for each baseline and 4-month follow-up assessment completed. Other assessments include weekly monitoring surveys, staff implementation time and processes, and costing data for cost-effectiveness analyses. These assessments are briefly described below and in detail in Rotheram-Borus et al [17].

Rapid Diagnostic Tests

The following rapid diagnostic tests are performed (see Shannon et al for details [47]):

1. HIV—Rapid test: Clinical Laboratory Improvement Amendments (CLIA)-waived Alere Determine HIV-1/2 Ag/Ab Combo fingerstick blood test for HIV-1/2 antibodies and the HIV-1 p24 antigen with a detection window of 12 to 26 days; results are available in 20 to 30 min. Once enrolled, potential acute HIV infection is assessed in batches using the Cepheid Xpert HIV-1 Qual Assay to detect HIV-1 total nucleic acids for acute HIV infection, or lab-based polymerase chain reaction (PCR) testing.
2. Chlamydia and gonorrhea—Food and Drug Administration–approved Cepheid Xpert CT/NG Assay PCR test using vaginal swabs from women, urine samples from men, and pharyngeal and rectal swabs from both women and men. Results are available in 90 min.
3. Syphilis—CLIA-waived Syphilis Health Check fingerstick blood test to detect treponemal antibodies with a 10- to 15-min time to completion.
4. Substance use—A multidrug urine test panel to detect the presence of marijuana, cocaine, opiates, and methamphetamine with result available in 2 to 5 min.
5. Alcohol use—The BACtrack breathalyzer to determine blood alcohol content over the past 48 hours.

Any study participants who test positive for HIV are immediately linked to care for treatment and offered enrollment in one of the ATN Comprehensive Adolescent Research and Engagement Studies (CARES) protocols for youth living with HIV, depending on stage of HIV infection determined by Fiebig stages 1 to 6 on HIV-1 antibody using Western blot test [45]. Participants testing positive for other STIs are provided immediate treatment by the study team, including partner therapy.

Questionnaires

Questionnaires are administered by an interviewer in a private room at partner sites or study offices, using Android tablets and take approximately 45 min to complete (see Rotheram-Borus et al for details [17]). Briefly, baseline questions cover lifetime and past 4 months; follow-up assessments cover the past 4 months. Questionnaires assess sociodemographic factors; health care access, insurance, and utilization; substance use; sexual behaviors; PrEP and PEP use; mental health; social media use; and locator information and consent to access medical records and to use social security numbers for locating efforts. Interviewers enter the participants' responses and rapid diagnostic test results in the CommCare mobile-Web electronic assessment and case management system that is cloud based and Health Insurance Portability and Accountability Act (HIPAA) compliant, by Dimagi Inc (see Comulada et al for details [44]). CommCare also manages and sends intervention and assessment text messages as part of the automated text-messaging and monitoring intervention (AMM).

Weekly Monitoring Surveys

The monitoring strategy is based on a weekly *Check-In* survey, which can be completed via text message or a Web link sent via email with a HIPAA–compliant RedCap version of the survey. Surveys assess the previous week time period with 7 questions on potential symptoms of acute HIV infection (yes/no), STI symptoms (yes/no), and number of days of feeling sad/depressed, sex without condoms, drug or alcohol use, not having a place to sleep or enough food; and miss taking medications (if taking medications). Participants receive a US $1 incentive per weekly survey completed, either in cash at their next 4-month follow-up assessment or on demand, including via electronic transfer (via Paypal, Venmo, or Zelle). Yes responses to HIV and STI symptom questions are reported to interviewers for follow-up risk assessment and rapid testing within 2 weeks. Reports on sadness/depression are monitored for potential follow-up and referral.

Outcome Measures

Our primary outcome is uptake and adherence to the HIV prevention continuum, according to the following measures, which will be analyzed individually and in sum (see Statistical Methods below):

1. Linkage to medical care reflected in a visit twice annually, at a minimum, to a health care provider
2. Consistent utilization of condoms, PrEP, or PEP
3. Participation in other HIV prevention programs and services
4. Repeat assessments for HIV and STI testing 3 times annually

Secondary outcomes include mental health symptoms, substance use, and housing security, which are hypothesized to impact primary outcomes as mediators or moderators of intervention effects.

Costing and Implementation Data

There are 2 types of costs: costs of delivering the intervention and the additional costs incurred by participants for their use of health care services and services from other agencies (eg, use of health care services). Intervention costs are classified into 1 of 4 categories [48]: (1) capital equipment (eg, computers); (2) recurring supplies and services; (3) facility space; and (4) personnel, including fringe benefits. Costs in the first 3 categories are obtained from project records. Personnel costs include hours and wages of staff to design and deliver the interventions, including peers, coaches, supervisors, facility charges, software costs, and short messaging service (SMS) and other social media costs, messaging and mobile app data costs, additional time in coaching and supervision, and server hosting. Personnel time is estimated from time reported on time sheets for hourly employees and budgeted time for other staff and investigators. Time spent on specific activities for hourly staff (eg, coaches and interviewers) is assessed in detail over 1-week periods quarterly using the Time It app [49] on their study-issued Android smartphones. Recorded time over 1-week periods is extrapolated to cover total time over the study period. The costs of additional services are derived from respondent reports on utilization and medical records and are estimated using publicly available data. Research-specific costs, such as incentive payments, informed consent, assessments, and software adaptation for survey tools, are excluded from total costs. All cost data are price-adjusted back to the first year of the study, using the medical care component of the consumer price index.

Intervention Development

Youth Advisory Boards

Consistent with the model of community-based participatory research [50,51] and requirements for all ATN studies, YABs reviewed and provided feedback on all study protocols and interventions before study launch and are involved on an ongoing basis to ensure that interventions are continuously improved. In particular, YABs reviewed and provided feedback on adaptations or cutting of every text message in the libraries of existing text messages (details below). YABs also provide topics of interest for peer support discussion boards and its associated website content and branding. YABs comprise about 10 seronegative YAHR and youth living with HIV (undisclosed) in both Los Angeles and New Orleans and reflect the diversity of the youth in both cities.

Text-Message Libraries

The existing libraries of HIV prevention messages adapted by the YAB include: (1) Project Tech Support [52], which has developed over 600 theory-based text messages specifically for methamphetamine-using MSM focused on reducing sexual risk behaviors and methamphetamine use and increasing ART use and adherence for those who are living with HIV; (2) the UCARE4LIFE text-message library from the Health Resources & Services Administration HIV/AIDS Bureau [53], which were designed for youth living with HIV but adapted for YAHR for this study; and (3) the PrEPTech library from youth+tech+health focused on increasing uptake and adherence to PrEP [54]. These libraries formed the basis of the initial text-message content for adaptation in collaboration with the YABs. Message libraries have been tailored for 2 different risk profiles—LGBTQ and heterosexually identified youth. Research indicates that messaging interventions based on cognitive behavioral theory are more likely to be successful [52,55-57]. In particular, text-message libraries from Project Tech Support [52], which form the majority of messages adopted for this project, were based on Social Support Theory [58-60], the Health Belief Model [61-63], and Social Cognitive Theory [64,65].

Intervention Conditions to Optimize the HIV Prevention Continuum

Condition A/Arm 1: Automated Text-Messaging and Monitoring Alone

AMM is a relatively low-cost and scalable intervention that could be diffused nationally. AMM is provided to all study participants across study arms as part of the enhanced standard of care and ethical requirement to provide prevention information to high-risk youth per ATN guidelines.

Daily Texts to Inform, Motivate, and Refer Youth to Services

Messages are sent daily, at times selected by each participant. Some evidence suggests that several text messages each day might be required to have an impact on behavioral outcomes [66-68]; therefore, up to 5 messages are sent per day in 5 content streams outlined in Table 1. Participants may opt-out of and opt-in to each of the 5 message streams at any time during the study by contacting interviewers and by updating preferences at each follow-up assessment when interviewers prompt participants and collect feedback on message experience. If a participant texts *STOP*, the SMS gateway provider (Twilio) stops sending all text messages. Messages are sent every day on health care (eg, medical, dental, and provider interactions), wellness (eg, mental health, diet and physical activity, social support, housing, jobs, and education), and medication reminders (if taking). Messages on sexual health and substance use are sent on Thursdays, Fridays, and Saturdays, a design decision based on YAB guidance to minimize messaging burden for these sensitive topics while maximizing impact on days when risk behaviors are most likely.

Table 1. Automated text-messaging and monitoring intervention daily text message examples.

Text message type and Risk Profile: MSM[a]	Risk Profile: non-MSM
Health care (70 messages)	
Your health is important.	First things first. Are you doing everything you can to stay healthy?
Vaccinations can be injections, drops or sprays. They are a proven way to prevent disease and keep you healthy.	It's your life we're talking about. Be a part of EVERY decision about your health care.
New in the area? Make sure to get a new doctor close by! Go to http://tinyurl.com/js8mqa6 to find free clinics close to you.	Get nervous talking to your provider? Write down any questions you have and bring them with you so you don't forget.
Wellness (70 messages)	
Friends can be good medicine. If you need to talk, give a friend a call.	Have you laughed today? Laughing is a great form of stress-relief, get some laughs in your day!
Gay Pride is taking care of yourself.	It's OK to ask for help.
Been inside all day? Get outside and soak up some quick sun for a boost of energy.	A budget can help make sure you have enough money every month. To learn more, visit http://tinyurl.com/kx8bxp2
Sexual health (100 messages)	
If your partner wants to get tested for HIV, text KNOWIT (566948) and enter their ZIP code. KNOWIT will text back a nearby testing site.	Left untreated, some STIs can cause health problems that make it hard or impossible for a woman to get pregnant. Visit http://1.usa.gov/1dm9P0B to learn more.
Open relationship? Know your boundaries.	Make sure the only thing you "get" is laid.
Friction is the enemy. You can lube up every time.	Myth: Women can't give men HIV; Fact: Both men and women can get HIV from vaginal and anal sex.
Substance use (90 messages)	
Stay in control—people who are drunk or high take more risks.	When was the last time you had sex sober?
Drinking alcohol can take a toll on your body. Take care of you!	Only take a fixed amount of cash out (and no cards) if you want to control how much you drink.
Spending too much money on Tina?	Going out tonight? Be safe. Party smart.
Medication adherence (100 messages)	
Reminder. It's going to be a great day.	It's that time again.
When you take your meds regularly, you're in control.	Take care of yourself today.
Is your stomach feeling a little off after taking your PrEP? Try taking your pill with food to ease possible stomach discomfort.	Where are you storing your PrEP? Your hot car or fridge can damage the medication-- keep it at room temperature.

[a]MSM: men who have sex with men.

Weekly Monitoring

In addition to monitoring for HIV/STI symptoms for follow-up testing and linkage as described above for study assessments, monitoring also functions as self-monitoring. Self-monitoring is a key skill for self-management and a core construct in social cognitive theories [69-71]. Preliminary studies on mobile self-monitoring demonstrated feasibility and acceptability [72,73], validity and reliability [74,75], compliance (ie, protocol adherence) [76], and user preferences. The efficacy of theory-based mobile self-monitoring to support self-directed self-management has also been demonstrated [74,77-80]. Self-monitoring by mobile or Web apps to support motivational interviewing to reduce substance use and sexual risk has demonstrated efficacy with substance users, persons living with HIV, and persons at high-risk for HIV infection [81-86]. In this study, weekly text-messaging monitoring surveys remain open for response for 48 hours. In the cases of nonresponse, CommCare automatically sends a follow-up prompt 24 hours after the initial prompt. After 2 weeks of nonresponse, interviewers initiate follow-up to assess current status of the youth. If participants are nonresponsive to text messages or opted-out via the SMS gateway by texting STOP, emails are sent instead with a weblink to a RedCap version of the survey.

Condition B/Arm 2: Automated Text-Messaging and Monitoring and Online Peer Support Groups Via Private Social Media

Peer Support groups are a low-cost strategy to enhance prevention and adherence interventions. Relationships have been shown to be motivating and increase engagement and retention in care for a range of chronic diseases [87-89]. Adolescence, in particular, is a developmental period where the influence of peers is crucial [90]. Almost every EBI for HIV prevention in the CDC's Compendium of EBI has a peer support component [91]. Several studies or online peer support groups with young minority MSM and LGBTQ youth have demonstrated preliminary efficacy for reducing HIV risks [92-94]. In addition, 2 other online peer support group interventions combined with peer paraprofessional coaches via

private Facebook groups (no longer feasible because of privacy and IRB concerns) found increased requests by MSM for HIV home test kits in Los Angeles [95] and increased clinic-based HIV testing in Peru [96]. Although a recent meta-analysis of 31 RCTs did not find significant benefits for electronic peer-to-peer interventions alone [97], the review noted that studies combining peer support with other interventions found some evidence for efficacy on the basis of associations between greater use of peer support via social media, indicating a dose-response association [98-100]. Therefore, this study is examining online peer support groups, moderated by paraprofessional near-peer coaches, in conjunction with AMM and also in conjunction with coaching in study Condition D/Arm 4.

Participants randomized to online peer support groups (Conditions B/Arm 2 and D/Arm 4) are invited to participate in a private Web discussion board hosted on Muut. Muut is an open-source discussion platform that is mobile- and desktop-friendly. Users can personalize their Muut profiles using avatars and photos, and content created can be continually reorganized according to new and relevant *channels* (eg, for a PrEP channel and mental health-related channels). Muut includes social media features such as *likes* and emojis, and multimedia content by embedding the forums in the study website. Private messaging functions are disabled because of IRB concerns around communication among participants that cannot be monitored or moderated. Participants are required to register and request access to join, which is facilitated by detailed screenshot instructions sent by SMS and in-person by coaches at the recruitment sites. Coaches and project coordinators review access requests to ensure that only study participants are attempting to join the forums and that their usernames do not compromise their anonymity by including their names. In total, 2 forums are available, 1 for LGBTQ-identified youth and another for heterosexual-identified youth.

Coaches and intervention coordinators seed discussions by creating and posting blogs, polls, and discussion topics twice a week on popular culture and general health and wellness to increase engagement (on the basis of YAB feedback), in addition to HIV prevention continuum themes (health care, PrEP, PEP, condom use, STIs, and HIV) and secondary outcome themes (mental health, substance use, and housing), including referral, resource, and services information. Coaches and coordinators also moderate the forums throughout each day to ensure that ground rules are followed, delete inappropriate posts, post correct information, and engage with and reward participant-initiated content. Participants are given warnings and removed from the discussion board if they post inappropriate content 3 times after receiving feedback for each occurrence, which includes: solicitations for sex and drug use; racist, homophobic, or other stigmatizing content; pornographic content; *trolling* inflammatory remarks or personal insults.

Participants are incentivized to participate and support their peers by posting questions and new discussion threads and responding to content posted by peers and coaches, such as sharing experiences and advice. Participants receive US $10 in cash or electronic transfer for initiating or responding to posts 3 times in a week, for up to 16 weeks over follow-up period.

Condition C/Arm 3: Automated Text-Messaging and Monitoring and Coaching—Strengths-Based, Youth-Centered

There are 2 levels of coaching engagement and overall functions in this intervention condition anticipating youths' varying preferences and needs over time; patient navigation (ie, services and resource referral and linkage) and more intensive, strengths-based, youth-centered, goal-focused coaching. *Patient Navigators* are one of the primary strategies advocated to link and retain high-risk populations to prevention and treatment services. Similar to navigators used for chronic diseases [101-103], the CDC recommends that patient navigators can help optimize the HIV prevention continuum [104,105]. Patient navigation involves a paraprofessional or experienced peer helping persons link to health care and services, assist with insurance, problem solve barriers to care, and provide supportive counseling and follow-up to motivate engagement and retention in health and prevention services. Coaching is based on the strengths-based model [106], which has demonstrated positive impact with homeless youth [107] and persons living with HIV [108]. Critical components of the model include identifying personal and interpersonal strengths rather than deficits and then setting, problem-solving, and accomplishing long- and short-term client-centered goals selected by participants in collaboration with coaches with a focus on hierarchies of needs (housing, food, and employment) as well as programmatic priorities.

In this study, coaching formally begins with a strengths-based assessment, an approximately 45-min open-ended interview that addresses 6 life domains: (1) daily living (survival needs such as food, housing, finances, and employment); (2) physical health (non-HIV related health problems); (3) health care; (4) social relationships (including social support, disclosure, and stigma); (5) mental health; and (6) HIV risks (substance use and risky sexual behaviors). Youth are asked to identify their current status within each domain, as well as strengths and challenges in each area. This assessment guides the development of personalized goals. Each youth has a maximum of 3 goals at any given time. The coach and youth identify a primary goal to address following the session including identification of resources and skills needed to achieve the goal (eg, problem-solving and coping skills). Typically, long-term or lofty goals must be broken down into smaller short-term *SMART* goals (ie, specific, measurable, achievable, realistic, and timely). Responsibility for goals is shared among the youth and coach depending on the nature of the goals. At each subsequent session, the coach *checks in* with the youth on goals set in previous sessions. As goals are accomplished, new goals are set. Goals not met are problem solved and adjusted to be achievable in successive approximation.

Coaches focus on the following priorities in their contact with youth:

1. Crisis support to address youths' immediate priorities and needs, particularly housing, which are typical barriers to engaging in other health-promoting activities
2. Completion of a strengths-based assessment session, including goal setting
3. Problem-solving priorities and facilitating linkages to prevention services, health care, and other services and providers (eg, Case Managers at recruitment sites, nearby agencies, or providers for mental health, substance abuse, housing, jobs, school, in conjunction with Case Managers, if available)
4. Appointment coordination, scheduling, and reminders
5. Follow up with clients to give a rewarding message for attending appointments (eg, Great job attending your appointment!) or to problem solve barriers if patient missed an appointment

Although the ultimate aim of this study's coaching intervention is to improve HIV prevention continuum, coaches also aim to address the hierarchy of needs and secondary outcomes that are hypothesized to influence prevention outcomes, such as homelessness, employment, mental health, and substance abuse. More details on the coaching intervention are provided in a publication for a sister protocol for youth living with HIV [47].

Coaching represents the most intensive person-mediated strategy in this study; however, coaches use a variety of means of communication and interaction on the basis of participant preferences and responsiveness. These include text messaging, phone calls, social media private messaging, video chat, email, and in-person contacts. In particular, in-person contacts are accommodated to meet youths' preferences for initiating a coaching relationship and building trust and rapport, including on an ad hoc basis at recruitment sites with coaches being on site to engage participants who are nonresponsive to initial text message and telephone contacts.

Importantly, and as noted in the introduction, this is not a manualized or scripted intervention. Instead, it is based on training, monitoring, and supervision using common practice elements or skills identified across EBIs for youth prevention and behavioral health [109,110], in addition to the priority topic domains of the project. The practice elements used are engagement/rapport building (including setting expectations), goal setting, problem-solving, praise, self-monitoring, assertiveness communication, triggers, relaxation, social support networking, positive activities/alternatives, setting up rewards, positive self-talk, monitoring (by coaches), emotional regulation, relapse prevention, modeling/role-play, and referrals. The content domains are daily living (housing, food, and employment), social relationships, sexual behaviors, PrEP/PEP use, anxiety, depression, other mental health, substance abuse, physical health, violence, and crisis support. Training modules and monitoring tools are based on these practice elements and content domains.

After every contact with a participant, whether a full coaching session or brief navigation interaction or follow-up, the coach completes a brief interaction log or monitoring log using the CommCare mobile-Web app on smartphones, tablets, or Web-connected computers. The log forms record the practice elements used and content domains covered during the interaction. This activity logging functions to prompt coaches to use the skills and address the content priorities of the intervention while simultaneously providing fidelity monitoring to inform supervision and for data analyses.

Training and Supervision

Coaches are near-peer, bachelor's-level paraprofessionals and of similar age, ethnicity, gender, and sexual identity to the participant populations. In addition to the components of the strengths-based model, practice elements, and content areas outlined above, coaches are taught the foundational theory of behavior change (people change slowly over time with small steps and with opportunities and rewards), the shared principles of behavior change (Be Prepared; Act on facts, not feelings). Coaches participate in weekly, cross-site supervision via in-person and videoconference meetings to debrief and jointly problem-solve logistical and clinical challenges with the principal investigator and supervisors. The practice elements are reviewed and reiterated during weekly training and learning community calls with all coaches as their toolbox for addressing the core content areas to be addressed. In both Los Angeles and New Orleans, there are local, on-call clinical psychologists for participants in crisis and who also provide weekly clinical supervision and ongoing booster training to coaches.

Condition D/Arm 4: Automated Text-Messaging and Monitoring and Peer Support Via Social Media and Coaching Automated Text-Messaging and Monitoring

This intervention condition delivers the combination of the above interventions, which enables estimation of the cumulative or synergistic effects of what might be considered an ideal model of support for high-risk seronegative youth to optimize their engagement and retention in the HIV prevention continuum.

Data Analysis

Analyses are described according to each of the study aims.

Aim 1: To Assess the Independent and Synergistic Effects of the Interventions on the HIV Prevention Continuum Outcomes

Multilevel models (MLMs) will be used to test the impact of the intervention on HIV prevention continuum indicators and secondary outcomes over time shown in Textbox 1 in the Background section. MLMs are needed to account for the hierarchical nature of the data and model correlations between repeated observations to properly estimate standard errors on regression coefficients. MLMs are flexible in handling discrete outcomes, such as binary HIV-prevention-continuum indicators (yes/no) and continuous outcomes, such as mental health measures. The MLM analyses will contain main effects for peer support ($PEER_i$) and coaching ($COACH_i$), as well as a 2-way interaction between peer support and coaching compared with AMM alone. This model parameterization will allow us to test independent effects of peer support and coaching and their synergistic effects on outcomes. MLMs contain interactions between TIME and intervention effects to test for changes in outcome levels between intervention arms over time (our primary goal). Equation 1 shows a random intercept (RI) model that will provide a starting point in the modeling process. Let

Y_{it} be an outcome for person i at time point t and let η_{it} be a link function for outcome Y_{it}, such as a logit link for binary prevention-continuum indicators. An MLM with a random effect λ_i to capture correlations between repeated observations for each person is expressed as:

$$\eta_{it} = \beta_0 + \beta_1 PEER_i + \beta_2 COACH_i + \beta_3 TIME_{it} + \beta_4(PEER_i \times TIME_{it}) + \beta_5(COACH_i \times TIME_{it}) + \beta_6(PEER_i \times COACH_i \times TIME_{it}) + \lambda_i. \quad (1)$$

We will also fit MLM with other covariance structures that we have used in previous HIV intervention studies, including RI and slope (RIAS) and autoregressive covariance structures. The covariance structure with the best fit statistics will be selected. Covariates for demographics and other background characteristics may need to be added to Equation (1) if imbalances are found across intervention arms at baseline.

As a first step, MLM will be fit to each primary outcome and secondary outcome and intervention effects for each outcome will be evaluated separately. We will also evaluate the overall impact of the intervention across binary indicators for optimization of the prevention continuum utilizing a strategy employed by this team to analyze multiple outcomes with one overall statistic, to reflect if there is an overall impact on multiple binary outcomes [111]. Analysis of multiple outcomes through separate regressions increases the probability of finding a significant intervention effect by chance (ie, type I error is inflated). Therefore, we will properly adjust the type I error by conducting simulation studies to determine how many significant intervention effects are needed to declare an effective intervention. Simulation studies assume binary outcomes to be correlated to model a real-world phenomenon.

Aim 2: To Assess the Temporal Relationships Between the Primary and Secondary Outcomes

The temporal relationships between primary and secondary outcomes are analyzed using a bivariate-outcome MLM to examine bidirectional relationships between primary outcome and secondary outcome observations at different time points. One parameterization of the bivariate-outcome MLM that we have used in a previous HIV study to examine the time-varying relationship between HIV-transmission behaviors and mental health symptoms is the bivariate RIAS model [112]. This model is formulated through 2 separate MLM equations for each outcome, k=1,2, that are linked through random effects to model RIs λ_{0ki} and slopes λ_{1ki}. A covariance matrix is also modeled that includes correlations between random effects λ_{0ki} and λ_{1ki}. Correlation between random effects captures time-varying associations between outcomes, such as the correlation between the first outcome at baseline and the second outcome over time, and vice versa. Building off on Equation (1), the basic bivariate RIAS model is expressed as:

$$\eta_{kit} = \beta_0 + \beta_1 TIME_{kit} + \lambda_{0ki} + \lambda_{1ki} TIME_{kit}. \quad (2)$$

Aim 3: To Assess the Relative Cost-Effectiveness of the Interventions

The deployment of all HIV prevention strategies today must be based on the cost-effectiveness of peer support and coaching to automated messaging for HIV prevention continuum outcomes and reducing risk behaviors, substance use, and mental health problems. The cost-effectiveness analysis will compare the additional cost required, on average, to get an additional unit of outcome in the 2 person-mediated interventions (peer support and coaching) and in the attentional control (automated messaging) by calculating a cost-effectiveness ratio (CER) [113]. The CER is the difference in total costs of providing a person-mediated intervention versus automated divided by the difference in person-mediated outcome and automated outcome [113]. Primary outcomes of HIV prevention continuum and secondarily substance use and mental health are outcomes of interest. Costs are measured as:

$$CER = (C_{person} - C_{auto}) / (O_{person} - O_{auto}). \quad (3)$$

Analogous CERs will be calculated for peer support versus automated/attentional control, patient coaches versus automated, and for the combined peer support and coach versus automated control. CERs will be calculated at final the follow-up. We expect the person-mediated interventions to incur greater personnel costs than the automated ones. On the other hand, the person-mediated interventions may result in greater use of other mental health or drug treatment services than the automated group. These greater costs may or may not be offset by reduced costs of other services, such as incarceration, relative to the person-mediated groups. The CER answers the question of whether improvements in outcomes are worth any added costs. If the person-mediated interventions result in both better outcomes and lower net costs, it will be deemed *cost-saving*.

We conduct sensitivity analyses, as recommended by Gold [113] to estimate the extent to which the CER calculation is affected by differences in assumptions about the size of the differences in treatment effect. In particular, we determine how sensitive the CER is to assumptions that the difference in treatment effect is 1 SD below or above the mean estimated effect size. Similarly, we estimate the sensitivity of conclusions to costs that are 1 SD below or above the estimated mean.

Sample Size Calculations

Sample size calculations are conducted to detect changes in the probability of an HIV care continuum yes-no indicator, such as PrEP adherence, STI treatment, and 100% condom usage, over 7 time points (every 4 months over 2 years) for the MSM/transgender sample. Calculations show that we have at least 80% power to detect differences in the probability of an indicator as small as 10% to 16% at the last time point between 2 arms with 220 participants at 70% retention. Sample size calculations were conducted through simulation using the following steps. *First*, binary indicator values were simulated from a binomial distribution with the probability of an event (yes) on the basis of an MLM similar to Equation 1. Simulation regression coefficients were specified with baseline rates of 20%, 50%, and 80% to cover a range of care continuum rates we have encountered in previous HIV research and were set to be the same between intervention arms. We specified normally distributed random effects as we did in Equation 1 with an SD of 1.5, similar to what we have found in other studies. Finally, we assumed 30% loss to follow-up and used a sample size of 160 in each arm in simulations. In practice, we anticipated a much lower attrition rate but wanted to be conservative in our

sample size calculations. We simulated 1000 datasets for each of the baseline testing rates we specified and for different sample sizes for 2-arm comparisons. *Second*, we fit MLM models to each of the 1000 simulated datasets for differing combinations of parameters. *Finally*, power was estimated to be the ratio of the number of MLM with a significant difference between intervention arms over time divided by 1000. In the end, exploratory analyses will be conducted using the same analysis plan outlined above for 12-month follow-up that includes the cisgender-heterosexual participants.

Results

The project was funded in September 2016, and enrollment began in May 2017. Enrollment will be completed between June and August 2019. Data analysis is currently underway, and the first results are expected to be submitted for publication in 2019.

Discussion

Summary

The goal of this study is to test the efficacy and examine the cost-effectiveness and implementation of alternative models for delivering the CDC's guidelines for routine HIV/STI testing for YAHR of acquiring HIV and for delivering evidence-based interventions in modular elements instead of scripted manuals and in flexible technology-based delivery formats. The technology-mediated interventions for YAHR in this study aim to improve HIV prevention continuum of engaging in medical care, adopting PEP after HIV exposure or PrEP before HIV exposure, or a behavioral protection strategy, as well as repeatedly testing for HIV and STIs. Consistent access and utilization of medical care is a common challenge for adolescents and young adults [114], particularly African American and Latino youth [115]. Text messaging and social media technologies offer relatively low-cost modalities to scale interventions for adolescents nationally. The study design provides opportunities to assess the efficacy, potential synergistic or cumulative effects, and cost-effectiveness of the proposed automated and person-mediated strategies. The study assessments will also enable examination of time trends in onset and periodicity of risk, and the relationships between primary and secondary outcomes in bivariate outcome analyses. In the evaluation of each intervention condition's cost-effectiveness for the primary outcomes, we hypothesize that each intervention of increasing intensity (AMM, online peer support groups, and coaching) will have greater efficacy but that the added costs may not justify use at scale.

The mobile and social media intervention arms in this study build off the relatively nascent evidence base of internet, mobile, and social media interventions for populations at high-risk for acquiring or transmitting HIV [116-120]. Although technology-based assessments (eg, Web- and text-message surveys) [92,117] have demonstrated success with large samples in the thousands [121], mobile and social media technology intervention studies have tended to be in small scale by comparison [122]. Although several large-scale RCTs are currently underway to address HIV, most focus on a single technology-based strategy or a bundle of strategies in a single intervention arm, instead of a comparison of multiple strategies as in this study [120,123,124].

Youth present with a wide variety of issues that affect their risk for HIV infection. In addition, they can be extremely labile in terms of their emotional and behavioral reactions to life events as they undergo developmental changes, which affect their risk. The interventions in this study are available to youth over the duration of their study follow-up of 24-months for YAHR of acquiring HIV in the US (ie, MSM and Transgender youth) and 12-month of follow-up for other youth at elevated risk. This approach acknowledges variability and unpredictability of risk behaviors as adolescents experience developmental transitions. The interventions are available to prepare youth for transitions or to be available when transitions, crises, and risks occur. This is in novel contrast the last 30 years of the EBI movement for HIV prevention, which incentivized highly structured and increasingly brief interventions that demonstrated only short-term impacts on behaviors.

Strengths and Limitations

A limitation of this study is that study procedures and enhanced standard of care are relatively intensive interventions in and of themselves. Routine or indicated HIV and STI testing several times per year follows the CDC's recommendations for people at high risk of acquiring HIV; however, this study operationalizes this with active and incentivized follow-up, community-based testing, and immediate treatment provision and partner therapy for STIs without a clinical visit. Daily text messaging and weekly monitoring with follow-up add another layer of intervention that cannot be directly assessed in this study. These limitations result from several factors, including utility for study assessments, ethical standards for research with vulnerable adolescents and the ATN to provide some base level of prevention support, goals for the broader U19 to identify youth with acute HIV infection from this study's participants over time for a sister protocol [45], and to operationalize and examine costs and impacts of implementing CDC guidelines with community-based strategies [125]. Therefore, the potential efficacy and cost-effectiveness of the online peer support group and coaching interventions examined in this study should be considered within this context.

Conclusions

The study findings will be invaluable to inform future adolescent prevention interventions, not only for HIV but also in many other areas. This study will have policy implications for the allocation of resources to HIV testing resources in local communities, the uptake and scalability of interventions for youth, and innovative approaches for designing and diffusing EBI globally.

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Authors' Contributions

The following individuals contributed to the study as part of the ATN CARES Team in addition to authors: Sue E Abdalian, Jeffrey D Klausner, Robert E Weiss, Ronald Brookmeyer, Karin Nielsen, Yvonne Bryson, Tara Kerin, Chelsea Shannon, Ruth Cortado, Norweeta Milburn, Marguerita Lightfoot, and Wenze Tang.

Conflicts of Interest

None declared.

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Abbreviations

AMM: automated text-messaging and monitoring
ATN: Adolescent Trials Network
CARES: Comprehensive Adolescent Research and Engagement Studies
CBOs: community-based organizations
CDC: Centers for Disease Control and Prevention
CER: cost-effectiveness ratio
CLIA: Clinical Laboratory Improvement Amendments
EBIs: evidence-based behavioral interventions
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
LGBTQ: Lesbian, Gay, Bisexual, Transgender, and Queer
MLMs: multilevel models
MSM: men who have sex with men
NICHD: National Institute of Child Health and Human Development
PCR: polymerase chain reaction
PEP: postexposure prophylaxis
PrEP: preexposure prophylaxis
RI: random intercept
RIAS: random intercept and slope
RCT: randomized controlled trial
SMS: short messaging service
STI: sexually transmitted infection
YABs: youth advisory boards
YAHR: youth at high risk

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Toronto, ON, M5A 3Y5
Phone: (+1) 416-583-2040
Email: support@jmir.org