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Protocol

Comparison of Nutrigenomics Technology Interface Tools for Consumers and Health Professionals: Protocol for a Mixed-Methods Study

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Abstract

Background: Although nutrition interventions are a widely accepted resource for the prevention of long-term health conditions, current approaches have not adequately reduced chronic disease morbidity. Nutrigenomics has great potential; however, it is complicated to implement. There is a need for products based on nutrition-related gene test results that are easily understood, accessible, and used.

Objective: The primary objective of this study was to compare a nonpractitioner-assisted direct-to-consumer self-driven approach to nutrigenomics versus an integrated and personalized practitioner-led method.

Methods: This 4-month study used a mixed-methods design that included (1) a phase 1 randomized controlled trial that examined the effectiveness of a multifaceted, nutrition-based gene test (components assessed included major nutrients, food tolerances, food taste and preferences, and micronutrients) in changing health behaviors, followed by (2) a qualitative investigation that explored participants' experiences. The study recruited 55 healthy males and females (aged 35-55 years) randomized as a 2:1 ratio where 36 received the intervention (gene test results plus integrated and personalized nutrition report) and 19 were assigned to the control group (gene test results report emailed). The primary outcomes of interest measures included changes in diet (nutrients, healthy eating index), changes in measures on General Self-efficacy and Health-Related Quality of Life scales, and anthropometrics (body mass index, waist-to-hip ratio) measured at baseline, post intervention (3 and 6 weeks), and the final visit (week 9 post intervention).

Results: Of the 478 individuals who expressed interest, 180 were invited (37.7%, 180/478) and completed the eligibility screening questionnaire; 73 of the 180 invited individuals (40.5%) were deemed eligible. Of the 73 individuals who were deemed to be eligible, 58 completed the baseline health questionnaire and food records (79%). Of these 58 individuals, 3 were excluded either because they did not complete all required data collection forms or were later found to be ineligible. The final sample (n=55) was mostly female (75%), married (85%), and those who had completed postsecondary education (62%).

Conclusions: This study will leverage quantitative and qualitative findings, which will guide the development of nutrigenomics-based products in electronic formats that are user-friendly for consumers and health professionals. Although the

quantitative data have not been analyzed yet, the overwhelming interest in the study and the extremely high retention rate show that there is a great degree of interest in this field. Given this interest and the fact that nutrigenomics is an evolving science, a need for continued research exists to further the understanding of the role of genetic variation and its role and applications in nutrition practice.

Trial Registration: Clinicaltrials.gov NCT03310814; <http://clinicaltrials.gov/ct2/show/NCT03310814> (Archived by WebCite at <http://www.webcitation.org/6yGnU5deB>)

Registered Report Identifier: RR1-10.2196/9846

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KEYWORDS

nutrigenomics; nutrigenetics; genomics; epigenomics

Introduction

Background

Globally, chronic disease is a leading cause of death and morbidity that creates an ever-increasing economic burden on health care [1-3]. Diet is recognized as a significant modifiable risk factor in the development of chronic diseases such as diabetes, cardiovascular disease, certain cancers, and depression [4]. However, current nutrition approaches have not been adequate to effect the changes needed. Historically, nutrition science has presupposed that everyone absorbs and metabolizes nutrients similarly, and differences in nutrient requirements vary only by factors such as gender, age, and pregnancy or breastfeeding status [5]. However, one's nutritional status and the development of complex diseases also depend on the interaction of nutrients with DNA. Nutritional genomics, which encompasses nutrigenomics and nutrigenetics, improves on current health practices by enabling more tailored nutritional advice targeted to individual needs.

Nutrigenetics investigates the effect of genetic variation on nutrient bioavailability and metabolism. Nutrigenomics further investigates how nutrients and bioactive food compounds affect human health through epigenetic modifications [6-10]. For example, exposure to dietary deficiencies or excesses can result in changes in the epigenome, which alters gene expression profiles and other genome functions, leading to physical and mental health deterioration [11-13]. Therefore, by customizing an individual's dietary intake based on integration of life stage, current health status, and genome information, there is the potential to prevent or ameliorate the effects of conditions such as diabetes, metabolic syndrome, cardiovascular disease, cancer, and depression [7,14-17]. The application of tailoring one's diet from different information sources that include dietary-related DNA-based results, referred to as personalized nutrition, is becoming increasingly recognized as part of the next paradigm in health practice.

Although the advancement of nutrigenomics and personalized nutrition shows significant promise in improving population health, it also presents challenges. Nutrigenomics is more complicated to understand and deliver than current nutrition intervention approaches. Among health practitioners and government entities, there is concern about direct-to-consumer gene testing, particularly those which examine risk for disease, as it is unclear how individuals perceive and translate the

information given that there is no or little involvement from health professionals [18-20]. Busy health professionals, who may want to integrate nutrigenomics as part of their practice, may not have the time to learn the intricacies of the technology and the scientific background or think they have the competencies to explain findings and suggest modifications to individuals. Consumers have been largely left to find the information and interpret the findings themselves, leaving room for misinterpretation and misuse [20]. Despite these current issues, studies have shown that personalized nutrition based on gene test results improve dietary quality [15,21,22]. Therefore, the potential to use nutrition-related genetic information to optimize dietary interventions that can improve lives and health care costs is too great to ignore.

It is thought that to advance the application of nutrigenomics to personalized nutrition is going to require the training of health professionals who can work with consumers to appropriately provide guidance on the gene test results. In addition, there is a need to create technology-based interface tools that integrate currently accepted nutrition guidelines (eg, *Dietary Reference Intakes* [5]), phenotypic information about the person's current nutritional status (eg, anthropometry, physical activity), and genotype-directed nutrition based on rare or common gene variation [23]. This study proposes to compare standard and tailored personalized nutrition approaches based on gene testing and to elicit participant feedback about their experiences with the 2 types of interventions. The study results will be leveraged to generate new and tailored nutrigenomics tools that are digitally based for consumers and health professionals.

Objectives

The overall goal of this study was to investigate whether personalized dietary advice based on genotypic testing provided by a practitioner leads to greater dietary improvements and health outcomes compared with a nonpractitioner-assisted direct-to-consumer (DTC) self-driven approach. The main study objective was to compare a practitioner-facilitated personalized dietary approach that uses genotypic and phenotypic information with a DTC self-driven approach and their impact on changing participant's knowledge, motivation, and behavior related to diet and eating and the quality of their diet. It was hypothesized that significantly higher levels of knowledge, motivation, and behavior would be reported, and there would be increased diet quality changes in the group that receives personal DNA diet information and customized dietary advice (practitioner-led)

compared with the group that is provided personal DNA diet information (DTC self-driven approach) only. In addition to this primary objective, changes in self-efficacy were evaluated to determine whether it was a potential mediator/moderator of dietary changes, and changes in quality of life were assessed as a possible additional benefit to dietary changes. Focus group interview data were also collected to explore participants' experiences with using personalized nutrition tools and resources.

Methods

Study Design

A mixed-methods study was conducted, consisting of 2 stages: (1) an exploratory randomized controlled pilot study (2:1 allocation ratio) comparing standard DTC self-driven versus practitioner-facilitated approaches that use DNA-based diet information and (2) qualitative investigation of participants' experiences to examine the feasibility and acceptability of the intervention. The study protocol, including paper-based or Web-based data collection forms, was approved by Quorum Institutional Review Board (protocol #32220CDN/1). All participants were required to provide informed consent before enrolling in the study (online). The initial online consent form outlined the details of the study and requested consent to collect

eligibility screening information and if eligible consenting to provide baseline information. A time estimate of 15 to 20 min was indicated for completing the baseline questionnaire that was based on pilot testing of the online survey with study investigators and student volunteers (n=11). A second written consent form was reviewed at the first site visit with the participant, and they were invited a second time to consent to continued involvement in the study. On this questionnaire, they were given time estimates of 30 to 60 min for each onsite visit and 15 to 20 min to complete the online questionnaires between visits. The protocol was registered with the U.S. National Library of Medicine (trial registration #NCT03310814).

Study Participants and Setting

Participants included adults (aged 35-55 years) who were deemed eligible based on various criteria (Textbox 1). This age range was selected as people tend to typically notice changes in their health [24]. Sample size determination was based on estimated mean differences in diet quality scores used in a personalized nutrition intervention study [21], application of sample size for 2-sample comparison of means for repeated measures [25], and estimated rate of loss to follow-up of 10% (3/32). Using similar approaches and previous study results [26,27], we determined we would need a minimum of 16 participants per group to detect differences in self-efficacy and quality of life.

Textbox 1. Study participation: inclusion and exclusion criteria.

Inclusion criteria
1. Adults, aged 35-55 years
2. Ability to understand, sign an informed consent, and to provide a buccal DNA swab
3. Willing to improve health
4. Medically stable. Subjects with diet-related chronic disease can enroll provided that their condition was stabilized or well controlled for at least 6months at the time of the baseline visit
Exclusion criteria
1. Currently on a therapeutic or restrictive diet (eg, Atkins)
2. Diagnosis of 2 or more chronic diseases or unstable chronic disease as deemed by accepted clinical guidelines
3. Clinical diagnosis of any mental health condition
4. Any of the following conditions: HIV; chronic obstructive pulmonary disease; severe/uncontrolled asthma; cystic fibrosis; bronchiectasis; interstitial lung disease; chronic renal failure; colon or small intestine problem; liver or kidney disease; uncorrected hypothyroidism or hyperthyroidism in the previous 12 months; alcohol or drug dependence during the previous 12 months; current or former malignancy for which the participant has undergone resection, radiation therapy, or chemotherapy within previous 5 years
5. Currently enrolled or plan to be enrolled in another research study during the course of the investigation
6. Planned or recent (within the last 12 months) bariatric surgery
7. Current use of weight-altering medication for the purpose of weight loss
8. Investigators and their immediate families, with immediate family defined as a spouse, parent, child, or sibling, whether biological or legally adopted
9. Pregnant and/or breastfeeding
10. Current smoker
11. Body mass index ≥ 35
12. Any other health risk or condition that may put the participant at risk, or influence the results of the study or the participant's ability to participate in the study

Description of Study Groups

Participants, who were deemed eligible and provided consent, were randomized by a statistician independent to the study into either the intervention or control group. Those randomized to the intervention (I) group received their gene test result report (standard) and an integrated report in paper and online format that integrated information about their gene tests, dietary intakes in relation to the standards, and personalized DNA-based diet plan as recommended by current guidelines regarding personalized nutrition [23]. They also received counseling by a trained research registered dietitian (RD).

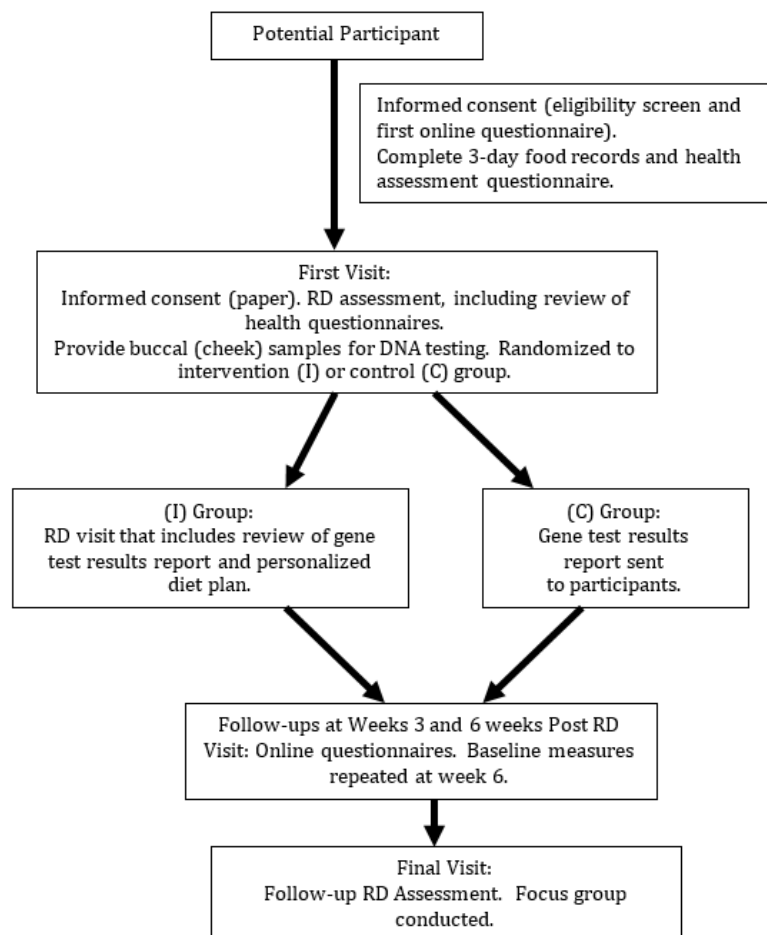
The counseling provided by the RD was based on both reports outlining their genes, markers, and variants. It included a corresponding DNA-based diet recommendation. For example, those who possessed the genotype that has been associated with increased risk of a health outcome were provided a “targeted” dietary recommendation. Subjects not possessing the specified risk variant received the current standard dietary recommendations [5,28]. In addition, the RD worked collaboratively with the participant to define 1 to 3 nutrition-related goals they would work on. Both groups received 3 follow-up emails (one every 2 weeks post intervention) with information about nutrigenomics as well as tips and reminders (eg, information about label reading) to help them reach their nutritional goals.

After the study is complete, participants randomized to the control (C) group will receive the intervention, that is, they will receive DNA-based dietary advice at the final study visit. Therefore, they will receive the same benefits, if any, as those who had the full intervention.

Study Visits

The study was conducted over 4 months and consisted of 6 points in time where participants either visited with research team members or provided information via online questionnaires (Figure 1). The online closed questionnaires (only study participants could access) were developed in FluidWare’s FluidSurveys [29] and in accordance with the Checklist for Reporting Results of Internet E-Surveys [30]. The online questionnaires were developed using standard measurement tools (see section Measurements) and protocols for nutrition assessment [31,32]. All data collection tools were pilot-tested among the study staff and student volunteers (n=11) for usability and technical functionality. For each online questionnaire, the numbers of pages (screens) were 12 or less, and participants could navigate it using back buttons and review functions. Participants were emailed instructions and the links to each online questionnaire at the appropriate time in the delivery of the study protocol. The study coordinator checked each questionnaire for completeness and for duplicate entries and followed up with participants as needed. In instances where participants had more than one questionnaire filled out, the most recent entries were used for analysis.

Figure 1. Overview of study design. RD: registered dietitian; I: intervention group; C: control group.



All online data were collected and stored in accordance with QUORUM guidelines to protect unauthorized access. A schedule of events is provided in [Table 1](#).

Recruiting/Screening: Online

Participants who entered the screening phase electronically signed an online informed consent form to grant permission to collect eligibility information and baseline health information (if deemed eligible). If the participant met the inclusion criteria, they were sent a 3-day food record to complete within 7 days (± 3 days) of their first site visit. In addition, they were sent the link to complete an online baseline assessment questionnaire that collected information about sociodemographics, their health (eg, presence of any health conditions, medications, supplements used), health-related quality of life (Short-Form 8, SF8), self-efficacy (General Self-Efficacy, GSE), physical and sedentary activities, food intakes (food frequency, food selection), and sleep quality.

Baseline Physical (On-Site) Visit

At the first visit, each participant met with the research team. They reviewed and signed a paper copy of the informed consent. The RD studied their online questionnaire information and did a nutrition assessment. Baseline measures of height, weight, and waist and hip circumference, based on standardized protocols [32], were performed. The 3-day food records were also reviewed to ensure completeness and accuracy.

At this stage of the study, a buccal swab cheek sample was obtained for gene testing. Buccal DNA samples were collected using Oracollect-DNA OCR-100 swabs (DNA Genotek, Ottawa, Canada). The RD collected the samples, identified with barcodes for confidentiality and blinding, and stored them between 15°C and 30°C. Participants did not eat or drink at least 30 min before obtaining their buccal swab. The samples were processed at the Clinical Genomics Centre at Mount Sinai Hospital in Toronto using Agena MassARRAY. Gene testing was done in 5 areas ([Table 2](#)) that were selected based on recommended evidence approaches to personalized nutrition [33].

Participants were informed that the processing time to receive results would be approximately 2 to 4 weeks. Between visits 2 and 3, a statistician independent to the study completed the randomization to the I and C group, using a computerized random generator.

Test Results and Diet Plan

Approximately 4 weeks (± 3 days) following the baseline visit, participants in the I group received a consultation visit with the RD who reviewed their individualized diet plan tailored to their health information and gene test results. Those in the C group were emailed their DNA test results report. Collection of information about adverse events, change in health status since the baseline visit, and concomitant medication was obtained.

Table 1. Schedule of events.

Activity	Screen	V1 ^a	Baseline (V2)	Consult (V3)	Follow-up assessments			Follow-up ^b
					4 weeks post consult (V4)	8 weeks post consult (V5)	Final (V6)	
Informed consent	✓ ^c	—	✓ ^d	—	—	—	—	—
Eligibility screen	✓ ^c	—	—	—	—	—	—	—
Food records	—	✓	—	—	—	✓ ^c	—	✓
Baseline ^e	—	✓ ^c	✓ ^f	—	—	✓ ^c	✓ ^f	✓ ^f
Registered Dietitian assessment	—	—	✓	—	—	—	✓	—
Anthropometrics	—	—	✓	—	—	—	✓	—
DNA buccal cheek swab	—	—	✓	—	—	—	—	—
Consults: report ^g & Report + DNA-based diet advice ^h	—	—	—	✓	—	—	✓ ^g	—
Follow-ups ⁱ	—	—	✓	—	✓ ^c	✓ ^c	—	✓
Focus groups	—	—	—	—	—	—	✓	—

^aV: visit.

^b4 weeks post final visit; control group.

^cOnline form.

^dPaper form.

^eBaseline: sociodemographics, Short-Form 8 (health-related quality of life), General Self-Efficacy, physical and sedentary activities, sleep quality (HealthMeasures' Patient-Reported Outcomes Measurement Information System), Food Frequency and Selection Questionnaire.

^fInformation reviewed.

^gControl group receives intervention.

^hIntervention group.

ⁱFollow-ups: income, social support, knowledge, behavior, action, adverse events, and concomitant medications.

Table 2. Description of gene test.

Area measured	Nutrient or food component tested
Diet management	Carbohydrates; cholesterol (high-density lipoprotein); cholesterol (low-density lipoprotein); fat—dietary; fat—stored; fat—monounsaturated; fat—saturated; insulin; protein
Weight response	Body mass index
Food tolerances	Alcohol; caffeine; gluten; lactose; salt; sugar craving
Food taste and preferences	Caffeine; carbohydrate; fat preference; protein preference; bitter taste; salt taste; sweet taste
Vitamins, minerals and essential fats	Vitamin A; vitamin B ₆ ; vitamin B ₉ (folate); vitamin B ₁₂ ; vitamin C; vitamin D; vitamin E; calcium; iodine; iron; omega 3; omega 6

Three- and Six-Week Online Check-Ins

At 3- and 6- weeks post intervention, both participants in I and C groups were sent their first follow-up online questionnaire with baseline measures repeated. Information about any adverse events (AEs), change in health status, and concomitant medication information was obtained. The only difference between the 2 questionnaires was that the I group questionnaire asked about whether knowing one's personal DNA helped the participant choose specific foods and meals to eat healthier. After the week 6 check-in, participants were sent food records to complete and bring to the final on-site visit. At the time of writing, the study is just in the completion of this phase.

Final Visit

At the final visit, the research team will review all data collected post intervention to ensure accuracy and completeness. The research dietitian will then conduct a repeat nutrition assessment. Participants in the C group will receive an individualized diet plan tailored to their health information and gene test results. Invitations to attend a focus group to solicit feedback about their experiences with the study will be extended. The interview guide for the focus group concentrates on collecting data about participants' responses to their gene test results and RD consultation, how they used their results, suggestions for improvements, and impressions about barriers and facilitators in using their results.

Outcome Measurements

All online measurement tools were pilot-tested with upper level university students and faculty in a science program. The outcome measures are described as follows:

Nutrition Outcomes

Three-day food records measured pre- and postnutrient intakes including daily eating patterns. Changes in caloric, macronutrient, micronutrient, and food groups will be measured and compared with national standards (eg, *Eating Well with Canada's Food Guide, Dietary Reference Intakes*). Changes in overall diet quality will be assessed using the Canadian version of the Healthy Eating Index [34]. Protocols for food record data collection will be derived from Health Canada nutrition survey procedures [35].

In addition to nutrient intake information collected from the food records, a food frequency questionnaire (FFQ) is included to assess for usual intakes and to validate the food record

information. The food frequency measurement tools were derived from Health Canada nutrition survey measures [35].

Nutrition measures also included food selection questions about types of food selected, dietary restraint, food insecurity, motivation to change diet, and eating behavior changes. These were based on validated measures such as the Three Factor Eating Questionnaire [36], Health Canada, Statistics Canada (eg, the Canadian Community Health Survey), and BC Ministry of Health surveys [35], as well as review of the research literature about measurements of motivation and dietary change and eating behavior changes. Some of these questions were developed by the research team and pilot-tested for comprehension and face validity.

Quality of Life and Self-Efficacy Outcomes

Measures of quality of life and self-efficacy were included to assess whether receiving DNA-based dietary information impacted one's general outlook and confidence to initiate changes. The measurement tools included the following:

Health-Related Quality of Life (HRQOL) SF-8 (Short Form 8)

The HRQOL-SF8 is a validated health survey that measures quality of life, functional health, and well-being; the 2 major scales, physical health and mental health, are included. The HRQOL-SF8 has well-established psychometric properties [37] and contains 8 items with a 4-week recall period. Each item has a 5- or 6-point response range. Physical component summary (PCS) and mental component summary (MCS) measures are calculated by weighting each SF-8 item using a norm-based scoring method given in the instrument guidelines. Higher summary PCS and MCS scores indicate better health. Scores above and below 50 are considered above and below the average in general populations [38].

General Self-Efficacy

The GSE is a 10-item self-report measure of self-efficacy, the belief in one's competence to cope with a broad range of stressful or challenging demands [39]. It includes questions about one's perceptions in the ease in which they stick to their aims and accomplish goals and to solve most problems if they invest the necessary effort. The GSE was included as a potential mediator/moderator variable related to any diet changes. It is a validated health scale correlated to emotion, optimism, and work satisfaction. Negative coefficients correlated to the GSE include depression, stress, health complaints, burnout, and anxiety. High reliability, stability, and construct validity of the

GSE scale have been confirmed, and Cronbach alphas obtained for the GSE scale have ranged from .86 to .94 [40].

Measures of Change in Knowledge, Motivation, and Behavior

Three questions developed by the research team were included to assess for changes in knowledge, motivation, and behavior related to DNA-based dietary advice. These were based on review of the research literature and included questions about the stages of change model [41]. The questions were pilot-tested before use.

Anthropometrics

Baseline measures of height, weight, waist circumference, and hip circumference based on standardized protocols [35] are included. Body mass index (kg/m^2) and waist-to-hip ratio will be calculated.

Covariates

Other relevant measures that can influence dietary intake and health behavior were assessed and controlled for. These included:

1. *Natural health product (NHP) usage*: NHP use (eg, vitamins, minerals, botanicals), which can influence nutrient intakes, is recorded at all study time points and included type, dose, and frequency of use. Participants were advised at baseline to keep any NHP use at the same dose and frequency throughout the study.
2. *Physical and sedentary activities*: To measure activity level, physical activity index (PAI) [42] was used. The PAI included questions about the frequency, duration, and intensity of participation in certain activities in the previous 3 months. The data on physical activity were combined to obtain the PAI, which represents the average daily energy expended on leisure-time physical activity, expressed in kilocalories per kilogram body weight per day. To calculate this index, the energy expenditure (EE) for each activity was first estimated (see [Multimedia Appendix 1](#) for details). The overall EE totals are used to categorize individuals as inactive (PAI <1.5 kcal/kg/day), moderately active (PAI 1.5 to <3 kcal/kg/day), and active (PAI ≥ 3 kcal/kg/day).
3. *Sleep quality*: The Patient-Reported Outcomes Measurement Information System Sleep Disturbance scale-short form [43] is used to assess sleep quality. The instrument is an 8-item self-rated questionnaire, which assesses sleep quality over the previous 7 days. Individual items are scored on a scale from 1 to 5, and scores are summed to yield a total raw score between 8 and 40, with lower scores indicating better sleep or a lesser degree of sleep-related impairments.
4. *Stress*: Because one's ability to deal with stress can impact dietary intake, 2 validated questions from the Canadian Community Health Survey [44] are included as covariates.
5. *Sociodemographics*: Standard determinants of health are measured that include sex/gender, age, relationship status, income, race/ethnicity, and perceived social support. The questions have been previously validated in studies such as the Canadian Community Health Survey.

Safety Reporting

At each study visit and online contact, participants were asked if they have experienced any AEs, change in health status, and/or had started any new medications or natural health products since the baseline visit. These data were captured using an AEs log and concomitant medication log.

Data Analysis

Quantitative Analysis

Food Intake and Nutrient Analysis

Nutrient analysis was conducted using ESHA—The Food Processor Nutrition Analysis and Fitness Software [45] and the Canadian Nutrient File [46]. Three-day food records were manually entered by a trained research assistant and cross-checked by the coinvestigators. Averages of the 3 days of nutrient values were used in the analysis.

Food Frequency Analysis

To calculate usual intakes (ie, \sum frequency weight \times nutrient content), individual-level reported frequencies of consumption (ie, per day, week, month, or year) for each of the FFQ items were multiplied with standard portion sizes [35], then with nutrient calculation algorithms based on the standard portion sizes. Next, usual daily food and nutrient intakes by question were derived based on summing nutrient or food intake levels for the macro- and micronutrients, prorating their frequencies accordingly (eg, divisor of 365 for a given nutrient value if frequency of intake for the food is yearly) to provide daily nutrient or food intake values. Finally, total daily values for a given nutrient will be calculated by summing the appropriate cluster of FFQ variables that contain the nutrient of interest.

Descriptive Analysis

Descriptive analysis includes reporting of means (\pm SDs) or medians (with interquartile range) depending on continuous variable distributions. Subject characteristics between the I and C groups will be compared. The distributions of nutrient intakes will be examined and appropriately transformed if they deviate from normality.

Inferential Analysis

Inferential analysis includes Student *t* tests, analysis of variance (ANOVA), and Fisher exact tests to compare differences between groups and pre- and postinterventions. Analysis of the primary outcome measures involve conducting a series of repeated measures ANOVAs, comparing scores for each of the groups on the primary outcome measures (ie, food intake) at baseline and 8 weeks after receiving gene test results. The second set of analyses will involve using repeated measures ANOVAs to compare the 2 groups on measures of the different covariates. All analyses will be done on an intent-to-treat basis (last observation carried forward) using StataCorp's STATA software [47].

Qualitative Analysis

Data from the focus groups will be transcribed by a professional transcriptionist and analyzed by research team members using interpretative thematic analysis. Initially, transcripts will be organized and coded as relevant passages of text. The focus

group interview content will be read repeatedly to identify patterns, preliminary concepts, themes, examples, and linkages to theory [48]. Transcript codes will be compared for identifying similarities and differences through discussions among team members to refine categories and themes. Using QSR International's NVivo [49], exemplars of coded text will be extracted. Interpretations will be reviewed by research team members and participants to check for descriptive and interpretive validity. Qualitative data will be reported based on thematic analysis derived from 3 independent reviews of the textual data.

Results

Four hundred and seventy-eight persons expressed interest in study participation in March 2017. Participants were invited sequentially from this list. This resulted in the study coordinator contacting a total of 180 of the 478 (37.6%) interested individuals who then completed the online eligibility-screening questionnaire. Given that most interested individuals were female, attempts were made to balance the sample by sex. Seventy-three of the 180 invited individuals (40.5%) were deemed eligible. Of those who were deemed to be eligible, 55 completed the baseline health questionnaire and food records (75%). The majority of participants are female, married, and have postsecondary education. To date, 3 participants were excluded (5%). This occurred before the first visit as they did not complete all required data collection forms or were later found to be eligible. No AEs have been reported.

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Authors' Contributions

IC drafted the manuscript, and all other authors reviewed and provided feedback on the drafts.

Conflicts of Interest

PL provides online nutrigenomics education.

Multimedia Appendix 1

Formula for calculating energy expenditure.

[[PDF File \(Adobe PDF File\), 17KB - resprot_v7i6e115_app1.pdf](#)]

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Discussion

Findings to Date

The high level of expressed interest and participant retention rate indicates that consumers are receptive to personalized nutrition approaches. The emerging science of nutrigenomics combined with personalized nutrition interventions are optimal means of providing dietary advice to the general population, genetic subgroups, and individuals. However, a demand for more sophisticated and user-friendly digital interface products that integrate a person's phenotypic information with the person's current nutritional status (eg, anthropometry, physical activity), current dietary intakes, and genotype-nutrition information are needed.

Conclusions

This study proposes to compare standard and tailored personalized nutrition approaches based on gene testing and to elicit participant feedback about their experiences with the 2 types of interventions. The study results will be leveraged to generate new and tailored nutrigenomics tools that are digitally based for consumers and health professionals. The data and products derived from this investigation are intended to help advance personalized nutrition approaches that could optimize individual and population health, create efficiencies in health service delivery, and generate savings in health care expenditures.

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Abbreviations

- AE:** adverse event
- C:** control group
- DTC:** direct-to-consumer
- EE:** energy expenditure
- FFQ:** Food Frequency Questionnaire
- GSE:** general self-efficacy
- I:** intervention group
- HRQOL:** health-related quality of life
- MCS:** mental component summary NHP: natural health product
- PAI:** physical activity index
- PCS:** physical component summary
- RD:** registered dietitian
- SF8:** Short-form 8

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Protocol

An eHealth Program for Patients Undergoing a Total Hip Arthroplasty: Protocol for a Randomized Controlled Trial

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Abstract

Background: Total hip arthroplasty is an effective surgical procedure commonly used worldwide for patients suffering the disabling effects of osteoarthritis when medical therapy is unsuccessful. Traditionally pre- and postoperative information for patients undergoing a hip arthroplasty has been provided by paper-based methods. Electronic health (eHealth) programs to support individualized patient education on preoperative preparation, in-patient care, and home rehabilitation have the potential to increase patient engagement, enhance patient recovery, and reduce potential postoperative complications.

Objective: The aim of this study is to compare the addition of an eHealth program versus standard care for pre- and postoperative education on patient outcomes for primary total hip arthroplasty.

Methods: One hundred patients undergoing a primary elective total hip arthroplasty will be recruited from a metropolitan hospital in Western Australia to participate in a 6-month parallel randomized control trial. Participants will be randomized to either the standard care group (n=50) and will be given the education booklet and enrolled to attend a 1-hour education session, or the intervention group (n=50), and will receive the same as the standard care plus access to an eHealth program titled "My Hip Journey." The eHealth program encourages the patient to log in daily, from 2 weeks prior to surgery to 30 days postsurgery. The information on the platform will be aligned with the patient's individual surgical journey and will include exercises to be completed each day for the duration of the program. The primary outcome measure is the Hip Dysfunction and Osteoarthritis Outcome Score, version LK 2.0. Secondary outcome measures include the EuroQoL EQ-5D-5L, a 5-level 5-dimension quality of life measure, and the Self-Efficacy for Managing Chronic Disease Scale. Data will be collected at pre-admission (presurgery) and at 6 weeks, 3 months, and 6 months postsurgery. A patient satisfaction survey will be completed 6 weeks postsurgery and Web-based analytics will be collected 6 months postsurgery. A cost-effectiveness analysis, using the intention-to-treat principle, will be conducted from the hospital's perspective.

Results: Enrollment in the study commenced in January 2018 with recruitment due for completion towards the end of the year. The first results are expected to be submitted for publication in 2019.

Conclusions: The outcomes and cost of using an eHealth program to support a patient's recovery from a hip arthroplasty will be compared with standard care in this study. If the eHealth program is found to be effective, further implementation across clinical practice could lead to improvement in patient outcomes and other surgical areas could be incorporated.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12617001433392; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373657&isReview=true> (Archived by WebCite at <http://www.webcitation.org/6yzoTuggx>).

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KEYWORDS

hip replacement; education; Web-based platform; eHealth program; rehabilitation; economic evaluation

Introduction

Osteoarthritis is a major disabling joint disorder worldwide, with the hip being the joint that is second most affected therefore resulting in pain, decreased function, and reduced quality of life [1]. Total hip arthroplasty (THA) is an effective surgical procedure that improves both joint function and quality of life for patients with hip osteoarthritis [2]. Internationally, there has been a significant increase in the number of THA procedures in the past ten years, and similarly each year the number of people in Australia undergoing hip arthroplasty has increased [3-4]. In Australia, in 2015, there were 44,710 hip arthroplasties (77.2% primary THA, 13.3% primary partial hip arthroplasty, and 9.6% for revision of hip arthroplasty). This represents a 2.6% increase in the number of hip arthroplasty procedures compared with 2014. Over half (59.7%) of all hip arthroplasty procedures in 2015 were undertaken in private hospitals [4].

For patients undergoing a total joint replacement, pre-admission, pre-operative, and postoperative patient education is essential. The mode of education delivery currently includes one-to-one verbal conversations, patient group sessions, educational booklets, and educational videos [5]. Many studies have explored the effects of these education programs on patient outcomes, including length of hospital stay, pain, functional abilities, knowledge, anxiety, and quality of life. A Cochrane review on pre-operative education for hip and knee replacements reported unequivocally that pre-operative education offers benefits over usual care in relation to or surgical outcomes, such as pain, function, and adverse events [6]. The review noted that pre-operative education may represent a useful adjunct with a low risk of undesirable effects. A more recent review linked pre-operative education to improved patient outcomes including lower length hospital of stay, higher rate of home discharge, lower readmission, and improved cost-effectiveness [6]. Additionally, other recent evidence not included in the Cochrane review demonstrated that the provision of pre-operative education is linked to a reduction in hospital length of stay [7-10].

An alternative forum for delivering patient education is through electronic health (eHealth). The World Health Organization defines eHealth as “the use of information and communication technologies for health” [11]. The introduction of eHealth programs to support individualized patient care at the pre-operative, peri-operative, and postoperative stages has the potential to improve patient engagement, self-care, and outcomes across the surgical pathway [12]. The implementation of eHealth programs enables a single source of credible information, which can be constantly updated as new information arises, and is

accessible to all patients irrespective of geographical location. Programs can be individually tailored to the patient, provide a platform for communication with health care professionals, provide electronic reminders to prompt patients, and can be used by other health professionals and carers to provide an enhanced continuity of care [12].

The aim of this study is to compare the addition of an eHealth program versus standard care for pre- and postoperative education on patient outcomes for primary THA. The hypothesis is patients who have access to the eHealth program will have better physical functioning post-THA compared to patients receiving standard care.

Methods

A prospective randomized controlled trial (RCT) will be conducted comparing an eHealth program to standard care for THA. Ethics approval was obtained from the participating study site (HPH505) and the University where the researchers are employed (19065).

Study Duration

Recruitment of the trial began in January 2018 and data collection is due to be completed within 12 months.

Setting

The setting of this study is a private metropolitan hospital in Western Australia with a focus on orthopedic surgeries. In 2017, there were a total of 848 hip surgeries performed in the hospital by 24 orthopedic surgeons. As the hospital is a private hospital, the surgeries are mostly funded through patients' private insurance.

Patients

Patients undergoing a primary elective THA will be invited to take part in the RCT. Patients will be screened and recruited during the usual pre-admission phone call conducted by the pre-admission nurse. Inclusion criteria are as follows: (1) the patient is undergoing a primary elective THA, (2) the patient is able to provide informed consent, (3) the patient is aged 18 years or over, and (4) there is a minimum lead-up time of three weeks prior to surgery. Exclusion criteria include the following: (1) the patient is undergoing a THA revision, (2) a bilateral THA, or (3) THA following a fractured neck of femur, (4) had a previous THA, (5) unable to converse in written or spoken English, (6) has no access to a Web-based device, and (7) has a risk assessment and prediction tool (RAPT) score less than six. The RAPT uses pre-operative patient factors of age, gender, pre-operative ambulatory distance, use of gait aid, community

support, and presence of a home caregiver to predict their need for extended care after a THA [13].

Randomization

One hundred patients will be randomized with a one-to-one treatment allocation to the intervention (n=50) or standard care (n=50) group at the time of consent. Allocation concealment in the order of recruitment will be conducted “off-site” after consent has been obtained. Permuted block randomization will be conducted to ensure an equal number of participants are allocated to each group per week. This will be conducted in weekly blocks of 10. Due to the nature of the research, blinding will not be possible for either the participants or the health care team. The researcher conducting the data analysis, however, will be blinded.

Standard Care

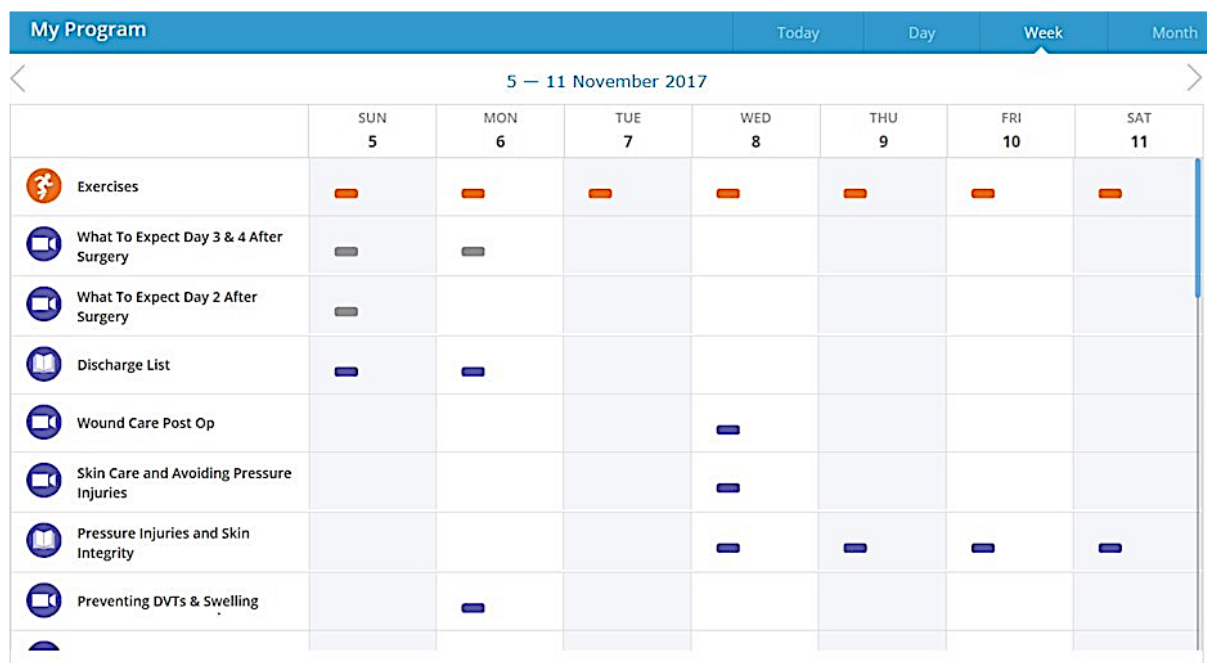
The comparator for the trial, namely standard care, is an Enhanced Recovery Program based on an orthopedic recovery program established in The United Kingdom [14]. It consists of participants receiving paper-based information, attending a 1-hour hospital-based face-to-face pre-operative education session, and a postdischarge follow-up phone call. The education session is presented by a registered nurse, occupational therapist, pharmacist, and physiotherapist and participants are encouraged to bring their support person to the session. Examples of the content in the paper-based information and education session include fall prevention, wound care, showering, healthy eating, returning to work, pain management, and selecting a personal alarm. The postdischarge phone call is conducted within one week of discharge by a registered nurse from the ward. During the phone call the nurse will ask specific questions about how the patient is coping postdischarge, including questions about pain management, wound healing, exercise and mobility, nutrition and hydration, bowel management, and how well the patient is managing daily living activities.

Intervention

The intervention for the trial is standard care as described above plus the addition of the eHealth education program. The eHealth program was developed specifically for patients undergoing a THA by a multidisciplinary team of clinicians, researchers, and consumer representatives. It provides information about the care requirements during the journey of a hip replacement, advice on well-being, and an exercise program. The information in the eHealth education program is for patients, support persons, relatives, and community health professionals and gives information on what to expect pre-operatively, whilst in hospital, postoperatively, and postdischarge.

Participants will access the eHealth program via a weblink after registration using a username and password. The program is designed to give participants continual access to information, at a time that suits them without them having to come to the hospital. It is recommended that participants use the program on a daily basis starting 2 weeks prior to surgery until 30 days postsurgery. However, the participants may have access to the program up to 4 weeks pre-operatively and will continue to have access until 12 months postsurgery. The eHealth program provides a suite of educational resources including fact sheets, videos, exercise videos, and email reminders about the pre- and postoperative care of a hip replacement. The resources are linked to the participants’ journey with a focus on personal wellbeing and its importance in the pre-operative and postoperative periods. Some examples of the resources included in the eHealth program are preparation for surgery, nutrition, pre- and postoperative exercise regimes, and medication management with additional information provided on walking aids and safety if living with pets. Each day, when the participant logs into their “My Program” window, it will display a list of videos and information as well as exercises that have been allocated for them to view or complete that day (Figure 1).

Figure 1. Screenshot example of patient’s “My Program” for one week.



Each exercise is allocated a specific number of repetitions and sets that the participant is required to perform, and this information is included with the information about the exercise for the participant. Participants have access to the health care team via the program's email for 4 weeks postdischarge and can invite their regular health care providers (such as their community occupational therapist and physiotherapist) or support person to be part of the program. The health professional team at the hospital can personalize the participant's program including the exercises by editing in number of sets and repetitions recommended for each exercise.

Intervention fidelity will be assessed using analytics built into the website. After a participant watches a video or reads information, they will be prompted rate it. The program will then mark it as read and record information about how long the participant spent on that piece of information. In addition, after the exercise videos are completed by the participant, they will

be prompted to mark them as complete. Automatically generated emails from within the program are sent on a regular basis to inform participants of the information available on the platform and provide instructions pre- and postoperatively. The health care team have access to the platform and can view the website analytics for each participant.

Outcome Assessment

Outcome measures will be collected at four time points, namely at pre-admission, 6 weeks, 3 months and 6 months after the surgery. [Figure 2](#) presents a flow chart of the recruitment and trial participation process and [Table 1](#) outlines the outcome assessments used in this study, as well as the collection time points for the assessments. Participants will be asked to complete the relevant assessments online and an email reminder will be sent to each participant when the assessment is due, followed by a reminder one week later.

Figure 2. Flow chart of recruitment and trial participation. RAPT: risk assessment and prediction tool; THA: total hip arthroplasty.

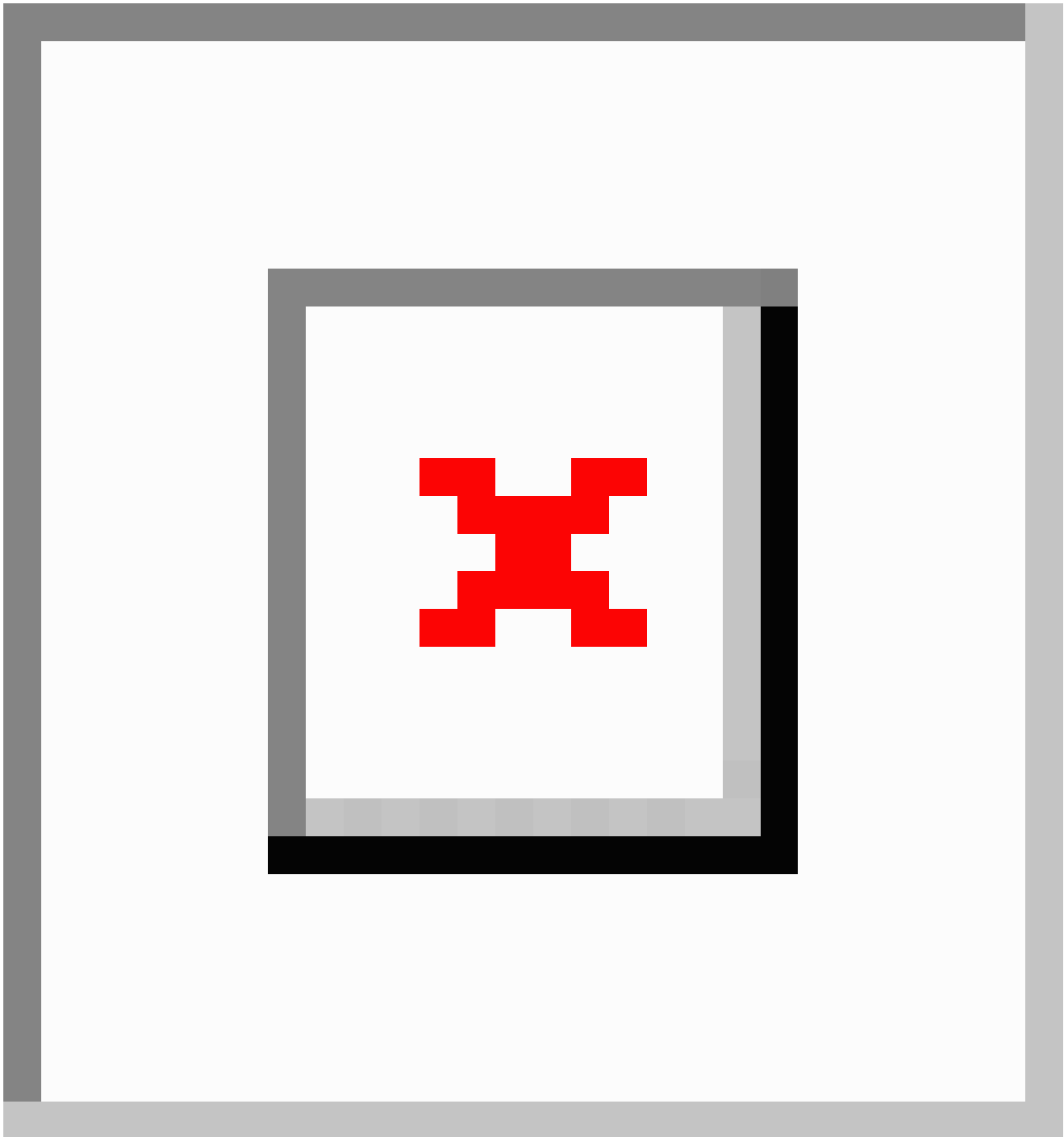


Table 1. Summary of primary and secondary outcome assessments and collection time points used in the study.

Outcome assessment	Pre-admission	6 weeks postdischarge	3 months postdischarge	6 months postdischarge
HOOS ^a	✓	✓	✓	✓
EQ-5D-5L ^b	✓	✓	✓	✓
SEMCD ^c	✓	✓	✓	✓
Satisfaction survey		✓		
Web-based analytics ^d				✓

^aHOOS: Hip Dysfunction and Osteoarthritis Outcome Score.

^bEQ-5D-5L: EuroQol EQ-5D-5L.

^cSEMCD: Self-Efficacy for Managing Chronic Disease.

^deHealth program only.

Primary Outcome

The primary outcome is patient-reported evaluation of symptoms and function limitations related to the affected hip (the hip undergoing surgery). The measure of this outcome is the Hip Dysfunction and Osteoarthritis Outcome Score (HOOS) version LK 2.0. The HOOS is a validated 40-item questionnaire where patients self-assess their hip across 5 subscales: (1) symptoms and stiffness, (2) pain, (3) function of daily living, (4) sports and recreational activities function, and (5) quality of life [15].

Secondary Outcomes

The secondary outcomes measures are quality of life, self-efficacy, patient satisfaction, and Web-based analytics. These will be assessed using the tools listed below.

The EuroQol EQ-5D-5L assessment will be utilized in this study. It is a 5-level 5-dimension standardized assessment tool, used to measure health-related quality of life. The 5 dimensions include: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The tool includes a visual analogue scale where participants are asked to rate their health on a scale from 0 to 100, where 0 means the worse health you can imagine and 100 means the best health you can imagine [16].

The Self-Efficacy for Managing Chronic Disease (SEMCD), is a validated tool consisting of six items on a 10-point scale measuring a participant's level of confidence in doing certain activities, 1 being "not at all confident" and 10 being "totally confident" [17].

Patient satisfaction with the program will be explored using a patient satisfaction survey developed by the research team. The developed survey comprises of 6 closed questions and 2 open questions for participants in both arms of the trial. Participants in the eHealth program will receive additional survey questions on the usability of the app, consisting of 13 closed questions and 3 opened-ended questions.

For participants in the eHealth program additional data on their utilization of the eHealth educational program will be collected through Web-based analytics. This will include information on the modules accessed, length of time spent on each module, and satisfaction ratings prompted within the program.

Economic Evaluation

A cost-effectiveness analysis comparing the developed eHealth program to standard care will be conducted from the hospital's perspective on an intention-to-treat basis. Direct costs will include the service delivery costs associated with each program (brochures, photocopying, and Web-based application fees) as well as the cost of follow-up care (the time spent by health professionals organizing and providing face-to-face sessions, replying to emails, making telephone calls, and managing and monitoring online content). Cost data will be collected from pre-admission through to 6 months postdischarge using hospital medical records. Outcomes will include changes in HOOS and quality of life (measured using the EQ-5D-5L). Incremental cost-effectiveness ratios (comparing the difference in cost between the eHealth program and standard care with the difference in the outcomes) will be calculated for HOOS and Quality Adjusted Life Years, and sensitivity analysis will be conducted on the key parameters.

Sample Size

Sample size calculations were conducted based on the primary outcome, the HOOS. Existing data were used to determine the minimal clinically important improvement [18] and SD [19]. Based on a power of 90% and 5% significance level, 42 patients per group are needed. To allow for a dropout rate of approximately 15%, a sample size of 50 per group is required. Therefore, the estimated required sample size for the study is 100 participants.

Statistical Analysis

Data will be reported in accordance with the Consolidated Standards of Reporting Trial (CONSORT). Mean (SD), median (interquartile range) and percentages will be used to describe the characteristics of the study group.

An analysis of covariance will be used to assess the primary outcome. The covariables will include age, gender, type of surgery, length of stay, RAPT score, and other comorbidities. Treatment effects will be calculated on the pre-to-post intervention outcomes at 6 weeks. Further analysis will be performed on the posttreatment effects at 3 months and 6 months postsurgery. The clinical treatment effect of each intervention group will be further analyzed using independent *t* tests, tests of medians, nonparametric tests, and chi-squared tests on

pre-to-post intervention changes across the range of outcome measures and patient satisfaction.

Results

Enrollment in the study commenced in January 2018 with recruitment due for completion towards the end of the year. We expect to achieve our goal of 100 participants. The first results are expected to be submitted for publication in 2019.

Discussion

The outcomes and cost of using an eHealth program to support a patient's recovery from a THA will be compared with standard care in this RCT. If the eHealth program is found to be effective, implementation into clinical practice could lead to further improvements in patient outcomes. Additionally, the findings of the study will support further research in the use of the eHealth program for other orthopedic surgical procedures such

as knee replacements. If the intervention is found to be cost-effective to the hospital, it could support resource efficiency.

Patients scheduled for a revision of THA, a bilateral THA, THA following a fractured neck of femur, or those who have had a previous THA are not included in the trial as their outcomes are likely to be different from those receiving a primary elective THA. A potential limitation of the trial is that in addition to patient self-reported outcome measures, more objective measures of function may have benefitted the trial (eg, the 10-meter walk test and 6-minute walk test). These tests are not included in the study due to the difficulty of conducting these tests pre- and postoperatively, particularly with patients living a distance from the hospital.

The findings from this study will contribute to the current body of literature on eHealth programs in orthopedic care and inform other health professionals on the outcomes of using an eHealth program.

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Authors' Contributions

All authors were involved in the conception of the study. KS and RS wrote the first draft of the manuscript, TS wrote the economic evaluation component. All authors reviewed and critiqued the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trial
eHealth: electronic health
EQ-5D-5L: EuroQol EQ-5D-5L
HOOS: Hip Dysfunction and Osteoarthritis Outcome Score
RAPT: risk assessment and prediction tool
RCT: randomized controlled trial
SEMCD: Self-Efficacy for Managing Chronic Disease
THA: total hip arthroplasty

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Protocol

Food Allergy Training for Schools and Restaurants (The Food Allergy Community Program): Protocol to Evaluate the Effectiveness of a Web-Based Program

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Abstract

Background: Food allergy is a growing public health concern. The literature suggests that a significant number of reactions occur in community services, such as schools and restaurants. Therefore, suitable training and education for education and catering professionals using viable and practical tools is needed.

Objective: The objective of this study is to evaluate the effectiveness of a Web-based food allergy training program for professionals working in schools and restaurants, designed to improve knowledge and good practices in the community.

Methods: Free learning programs which contain educational animated videos about food allergy were developed for professionals working at schools and restaurants. The learning programs comprise of nine 5-minute videos, developed in video animation format using GoAnimate, with a total course length of 45-60 minutes. The courses for professionals at both schools and restaurants include contents about food allergy epidemiology, clinical manifestations, diagnosis and treatment, dietary avoidance, emergencies, labelling, and accidental exposure prevention. Additionally, specific topics for work practices at schools and restaurants were provided. Food allergy knowledge survey tools were developed to access the knowledge and management skills about food allergy of school and restaurant staff, at baseline and at the end of the food allergy program. The courses will be provided on the e-learning platform of the University of Porto and professionals from catering and education sectors will be invited to participate.

Results: Data collection will take place between September 2017 and October 2017, corresponding to a 2-month intervention. Final results will be disseminated in scientific journals and presented at national and international conferences.

Conclusions: The Food Allergy Community Program intervention may improve school and restaurant professionals' commitment and skills to deal with food allergy in the community. Furthermore, this e-intervention program will provide an innovative contribution to understanding the impact of electronic health technologies on the learning process and the development of strategies for community interventions.

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KEYWORDS

food allergy; eHealth; community; schools; restaurants

Introduction

A food allergy is defined as a reproducible and specific immune response that occurs on exposure to a given food, leading to adverse health effects [1], affecting 2% to 5% of the population [2]. Currently, the primary treatment of food allergy is avoidance of the involved foods [1] but it is not uncommon for the lack of information to contribute to accidental dietary exposure [3]. Indeed, food allergy has emerged as a “second wave” of the allergy epidemic [4] and is now recognized as a public health problem, therefore requiring interventions at different societal levels. As a result, food allergy has been a problem under discussion in the legal and political sphere.

Studies show that a significant number of reactions occur in public places such as restaurants [5] and schools [6]. Additionally, they show that eating out is one of the key areas where food allergy patients feel there is a lack of information [7] and this results into an alarming feeling of insecurity when dining out. As a consequence of this insecurity, a fear of allergic reaction leads to patients limiting work, leisure, and social activities which include trips and meals, and this can have a wide impact on quality of life [8].

According to the literature, there is a consensus that there is a significant lack of information and education for the different stakeholders in the field of food allergy. Studies examining school personnel’s knowledge of food allergies have shown that teachers do not consider themselves sufficiently informed and prepared [9,10]. Moreover, the psychosocial impact of food allergies among school children is also a crucial and pressing issue. Several studies have shown an increase in cases of bullying with children with food allergy. A study by Lieberman et al found that 86% of food allergy pediatric patients in the United States of America report bullying [11] and, likewise, Muraro et al reported that, in Italy, 60% of children aged 8-19 years with a food allergy claimed that they were a victim of some form of bullying at least once in the past 2 months, a frequency which was twice as high than their nonallergic peers [12]. Thus, commitment and education of the stakeholders who provide food, deal with children and teenagers, and support their socialization are crucial for patients’ well-being in the school community [13].

When considering food allergy in restaurants, two studies have stated a particularly warring discrepancy between personnel’s knowledge about food allergy and their comfort level in providing a safe meal [14,15]. In a recent Environmental Health Specialists Network (EHS-Net) study on food allergy knowledge and attitude conducted by the Center for Disease Control and Prevention, the authors found that despite managers, food workers, and servers being generally knowledgeable about food allergies, critical knowledge gaps were present [16]. For example, more than 10% of the staff included in the study believed that a person with a food allergy can safely consume a small amount of the culprit allergen [16]. Additionally, staff reported a low confidence in their restaurants’ ability to correctly respond to a food allergy emergency [16].

When asked to identify barriers to learning about food allergies, restaurants’ personnel identified high training costs and time

constraints as the main barriers [17]. School personnel reported that video and internet resources are the best tools for them to learn about food allergy [18]. A Web-based training program would overcome the constraints identified by restaurant personnel and satisfy the requirements for school personnel and therefore constitutes a viable and practical alternative for training professionals from different sectors [19].

Previous computer-based intervention programs used in both schools [6,20] and restaurants [21] pointed to the feasibility and effectiveness of a computer-based training; however, these interventions are scarce, suggesting the need for more research in this area. The main aim of this study is to evaluate the effectiveness of a Web-based food allergy training program for schools and restaurants, which will promote food allergy knowledge and awareness in catering and education staff.

Methods

Study Design

The Food Allergy Community (FAC) program is an intervention program which intends to evaluate the effectiveness of Web-based food allergy training on food allergy-related knowledge and practices of professionals in the education and catering sectors. The project began in January 2015 and data collection will occur in between September 2017 and October 2017.

Participants and Data Collection

The target participants in this study are professionals in the catering and education sectors from Portugal, Portuguese-speaking African countries, and Brazil, who are interested in courses on food allergy management in restaurants and schools. The e-learning courses will be held on the University of Porto e-learning platform, *Academia UP*. The courses will be announced and widely disseminated through the media. Interested professionals in the catering and education industries will be asked to register through an online form, available at *Academia UP*, and provide their name, contact details, and occupation. All professionals who meet the inclusion criteria, namely teachers, educational assistants, health professionals, and tourism, hotel, and restaurant professionals who are currently employed in either the education or catering sector, as well as students, will be included in the study.

The e-learning platform is private, and access will be restricted by the research team providing individual credentials to the included participants. When participants first log in to the e-platform, they will be asked to read and complete the informed consent form in order to participate in the research. The consent form includes the purpose of the study, the level of data protection, and information on participants’ right to withdraw during the study. Additional instructional videos and materials will be available for participants to familiarize themselves with the online course procedures. After gaining informed consent, participants will be asked to complete a brief questionnaire on their demographic characteristics such as gender, region, educational background, occupation, and workplace specificities (eg, the classification of the restaurant or the school’s grade level).

After agreeing to join the study and acknowledging that the intervention includes both pre- and posttests to assess the participant's knowledge, participants will be randomly assigned into any of the 3 following groups: (1) the pretest group, (2) the posttest group, or (3) the pre- and posttest group. The existence of 3 groups will allow for the measurement of a possible interactive effect between pretesting and the intervention.

Ethics

This research was conducted according to the guidelines established by the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of University of Porto (24/CEUP/2016) and by the Portuguese National Commission of Data Protection (735/2017).

Food Allergy Knowledge and Practice Survey Tools

Two different Food Allergy Knowledge survey tools (one for each sector) were developed after an extensive review of the literature to determine food allergy knowledge and management skills of school and restaurant staff. They were based on previous questionnaires for restaurant [16,22,23] and school [9,24] staff, as well as other educational materials [25-27]. Initially, the questionnaires were reviewed by a panel of food allergy experts to optimize readability and question clarity, and to ensure they were at an appropriate difficulty level. Both questionnaires were tested by representatives of the target groups in a pilot study. Some questions were adjusted to improve questionnaires' validity, after which both questionnaires were converted to an online survey, therefore allowing the expected learning outcomes for the food allergy courses to be established (Textbox 1).

The questionnaires will be completed by the participants twice, before and after the training. The first questionnaire will assess the baseline level of knowledge of the target population which is important to generate a statistically valid baseline to determine the impact of the intervention. The questionnaire completed after completion of the e-learning modules will be used to determine the level of change in impact and outcome indicators between the baseline and final evaluations.

The first section of the questionnaire contains 20 multiple-choice questions with a single-best-answer (each scored one point if correct) to measure participants' knowledge and skills related to food allergies. The first 11 questions are common to both surveys and evaluate six different dimensions: epidemiology, diagnosis, symptoms and treatment, dietary avoidance, emergency procedures, food labelling, and the food allergies legal framework. The last 9 questions are specific to the target group and are different in the two surveys. For the questionnaire specific for school personnel, these questions evaluate good practice at the workplace, in particular the prevention of accidental exposure and awareness of bullying. For restaurant personnel, the questions evaluate the good practice in all stages of customer service, considering the prevention of cross-contact.

To evaluate whether the knowledge and acquired skills meet the learning outcomes foreseen for the course (Textbox 1), the questions will have both a theoretical domain (general concepts about food allergy and allergen avoidance) and a practical domain (regarding procedures to be followed in practical situations).

The second section of the questionnaire (the section specific to each sector) corresponds to questions regarding work-related practices and perceived responsibilities.

Textbox 1. The expected learning outcomes of the food allergy courses.

Learning outcomes for school and restaurant staff

- Understand the differences between food allergies, food sensitivities, and intolerances
- List the most common food allergens
- Recognize the symptoms of severe food allergic reactions and anaphylaxis
- Identify the diagnostic procedures of a food allergy
- Realize that an allergic reaction can be triggered not only by the consumption of the food but also by inhalation or skin contact
- Be aware that there is no routine treatment for food allergy, apart from dietary avoidance
- Be aware of how to avoid allergen exposure, including food labelling interpretation
- Respond safely and appropriately if an allergic reaction occurs
- Know the current legislation on the protection of the consumer with food allergy

Learning outcomes specific for school staff

- Prevent accidental exposure at school, namely in the canteen, classroom, playground, or bus
- Recognize bullying as one of the main psychosocial impacts of food allergy in children and teenagers

Learning outcomes specific for restaurant staff

- Communicate effectively with food-allergic customers to ascertain their needs
- Prepare and serve a safe meal to a food-allergic customer, considering the prevention of cross-contact

The responses will be addressed either through yes or no questions or a 5-point Likert-type scale, ranging from 1 (“Strongly disagree”) to 5 (“Strongly agree”), to examine whether personal experiences and training would impact food allergy risk perception and communication. After completing the Food Allergy Knowledge and Practice Survey Tools, participants will be able to join to the free online courses from the FAC Program.

E-Learning Food Allergy Courses for Schools and Restaurants

The intervention consists of an online asynchronous training program, which comprises of several lectures in video format about general concepts related to food allergy and food allergy management in schools and restaurants.

The training modules were developed based on the European Academy of Allergy and Clinical Immunology guidelines [28] and the Food Allergy Portuguese Guidelines, namely Food Allergy in Schools [29] and Food Allergy in Restaurants [30], published by Directorate-General of Health, in partnership with the Faculty of Nutrition and Food Sciences and the Faculty of Medicine at the University of Porto. Scripts for the videos were first developed and then translated into a video animation format, using GoAnimate (GoPremium; GoAnimate Inc, San Mateo, CA, USA), allowing for greater dynamics within the video and for participant engagement. The total course comprises of 9 modules, which contains 9 videos approximately 5 minutes in length. Therefore, the average time for completing the training is 45-60 minutes.

After considering the learning needs of the target audience, it was determined that the courses should both have a theoretical and a practical component (Table 1). The first six modules are similar for both courses and the lecture topics include definitions and concepts regarding food allergy symptoms, prevention,

diagnosis, and treatment. The last three modules are sector-specific, and address food safety and best practices in the workplace, covering questions regarding accidental exposure prevention and working tips.

The participants will have 4 weeks to complete the entire course (9 modules), and two to three modules will be launched per week. The platform does not restrict the number of times the modules are accessed during the course.

In addition to the course modules, the platform will also provide complementary readings and tools, including expert interviews and a live demonstration of how to use self-injectable epinephrine devices, as well as an interactive forum where participants can share their doubts and experiences. The participants who complete the course and obtain a grade higher than 9.5, out of 20 possible points, will receive a certificate of participation from the FAC Program.

Statistical Analysis

After the food allergy Web-based intervention program for schools and restaurants has been completed, statistical analysis of scores' improvement and differences between the three groups will be performed using SPSS Statistical Software (SPSS Inc, Chicago, IL, USA) and R software program (The R Foundation for Statistical Computing, Vienna, Austria).

Descriptive analysis (proportions) will be performed to characterize the participants and to summarize the answers to the Practice and Perceptions Survey Tools. To access the improvement on the participants' knowledge, General Linear Model for Repeated Measures test will be performed, allowing the 3 intervention groups to be compared. A *t* test will be conducted to compare the knowledge score means of the initial evaluation between the pre- and posttest group and the pretest group and the knowledge score means of the final evaluation between the pre- and posttest group and the posttest group.

Table 1. Modules included in the Food Allergy Online Course for Schools and Restaurants.

Module number	Module name
General modules	
1	Food allergy: General concepts
2	Food allergy: clinical manifestations, diagnosis, and treatment
3	Food allergen avoidance: Why it is so difficult?
4	Emergencies: What can I do?
5	Food allergen labelling
6	Food allergy prevention: Is it possible?
Modules specific for schools	
7	Food allergy in school I: Basics and canteen
8	Food allergy in school II: Inside the classroom and playground
9	Bullying and the psychosocial burden of food allergy
Modules specific for restaurants	
7	Communication and client's attendance
8	Cooking for allergic clients and meal service
9	Organization and storage: A helpful way to reduce the risk

Item response theory using the two-parameter logistic model will be performed to determine the quality (difficulty and discrimination) of the questions from the food allergy knowledge survey.

Results

Data collection will take place between September 2017 and October 2017, corresponding to a 2-month intervention. Final results will be disseminated in scientific journals and presented at both national and international conferences. Additionally, after the results of the study have been obtained, the courses could be permanently integrated into the training offered by the University of Porto, providing an added value for the formation of the community.

Discussion

Progress in e-learning and related technologies are creating the basis for developments in the education and teaching, with a gradual change from traditional and on-site teaching to a modern teaching, which is mainly Web-based [31].

In 2002, the United Nations Educational, Scientific and Cultural Organization (UNESCO) proposed Open Educational Resources, which are defined as “Teaching, learning, and research materials in any medium, digital or otherwise, that reside in the public domain or have been released under an open license that permits no-cost access, use, adaptation, and redistribution by others with no or limited restrictions” [32]. Beyond this concept, UNESCO also states that Open Educational Resources “provide a strategic opportunity to improve the quality of education as well as facilitate policy dialogue, knowledge sharing, and capacity building” [32]. Despite the influence of new information and communication technologies, educational interventions in the food allergy field are particularly scarce, and the effectiveness of training about food allergy has still mainly been demonstrated with face-to-face interventions.

Wahl et al [33] conducted a study where school personnel attended a training program which comprised of a 45-minute educational food allergy training presentation, which included key facts about food allergies, allergen avoidance, recognition of symptoms, and emergency treatment, and showed that the training program was an effective strategy for helping individuals who work with children to feel more confident in dealing with food allergies. In a similar study conducted by Polloni et al [9], an increase in school teachers' food allergy knowledge was observed after attendance at free multidisciplinary food allergy courses, which also highlighted the need for specific educational interventions. The same effectiveness in improving teachers' knowledge about food allergy was also found by Ravarotto et al in a study that presupposes the design, implementation, and monitoring of food allergy workshops [10]. Ultimately, the results of a study conducted by White et al [6], which aimed to evaluate the effectiveness of a computer-based learning module as an additional food allergy teaching tool for school staff, pointed

to the feasibility and effectiveness of this computer-based training, despite it being non-interactive.

Regarding studies on food allergy interventions for restaurants, Bailey et al designed and evaluated a food allergy educational intervention consisting of a 1-hour lecture about food allergy basics, accidental exposure, food labelling, emergencies, and proper communication with costumers [34]. At the end of the intervention, the authors concluded that food allergy training improved participants' food allergy knowledge and workplace practices. Considering the scarcity of studies in this field, we extended our literature search to related areas, for example, food safety programs in restaurants, aiming to review the methodology and results. Indeed, Dittmar et al developed a 2-hour online program to enhance the knowledge of food safety best practices which included scientific contents that met the criteria established by Texas Department of State Health Services (USA), along with interactive activities and handouts to reinforce key concepts in the program [21]. The authors concluded that the program was an effective tool to increase training outreach, given that there was a growing number of food service employees completing the course.

Finally, and more comprehensively, a review of massive open online courses related to health and medicine reported that there was potential to use massive open online courses to educate health care practitioners and students and to increase health literacy among the public [35].

Our study has some limitations, namely that (1) all participants require internet and basic computer knowledge, (2) the self-enrollment of the participants raises questions about the representativeness of the sample of participants and whether the participants are already interested and educated about food allergy, and (3) the higher possibility of drop-outs compared to on-site training. However, studies in both areas conclude that food allergy training and new information and communication technologies may be an effective tool to enhance knowledge in the fields of food allergy, food science, and food safety.

Additionally, the FAC Program will provide an innovative and important contribution to understanding the impact of new information and communication technologies on people's learning, which seems to be crucial for ongoing development of online training programs. Furthermore, it will provide more data on the basic knowledge of catering and education professionals, which is extremely useful since these data are scarce in Europe. The information on professionals' basic knowledge is not only useful for the continuity of the training in new editions of the program, but also for the development of better strategies for community interventions and new governmental and public health guidelines. Professionals may find that they can make use of this program as learning tool without great impact on their routine and budget, which could improve their commitment and their skills to deal with food allergies, leading to a greater awareness about food allergy and an increase on food allergic-patients' safety and integration in the community.

Conflicts of Interest

None declared.

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Abbreviations

EHS-Net: Environmental Health Specialists Network

FAC: Food Allergy Community

UNESCO: United Nations Educational, Scientific and Cultural Organization

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Protocol

Dental Home Visits for Caries Prevention Among Preschool Children: Protocol for a Cost-Effectiveness Analysis on a Randomized Control Trial

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Abstract

Background: In 2012, nearly 4000 children in Malaysia were referred to hospital pediatric dental services due to dental caries. Recent research has reported the effectiveness of dental home visits in preventing caries development in young children. Dental home visits (DHVs) are described as an ongoing relationship between the dentist and their patients, providing all aspects of a preventive oral health care program in the presence of the parents at home.

Objective: The objective of this study is to evaluate the cost-effectiveness of dental home visits and oral health information, in the form of educational leaflets, in preventing new caries development in young children, compared to those receiving only educational leaflets over a period of two years. Cost-effectiveness analysis will be used to evaluate the cost-effectiveness of dental home visits.

Methods: This is a collaborative project with the Oral Health Division of the Ministry of Health Malaysia. The Oral Health Division will provide access to a subsample from the National Oral Health of Preschoolers Survey which was carried out in 2015. The population of interest is children aged 5 and 6 years from kindergartens in the Selangor state of Malaysia. The study adopted a societal perspective for cost-effectiveness analysis and all types of resources that are of value to society will be included in analyzing the costs; such as cost to the patient, cost to the provider or institution, and indirect costs because of loss of productivity.

Results: The trial has been approved by the International Medical University Malaysia's Joint Research and Ethics Committee (Project ID: IMU R157-2014 [File III – 2016]). This trial is currently recruiting participants.

Conclusions: The number of young children in Malaysia who have been referred to the hospital children's dentistry service for severe caries is disturbing. The cost of dental treatment in young children is high due to the severity of the caries which require an aggressive treatment, and the need for general anesthesia or sedation. This study will provide information on the cost and effectiveness of DHVs in caries prevention of young children in Malaysia.

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KEYWORDS

cost-effectiveness analysis; dental home visits; caries prevention; preschool children

Introduction

In Malaysia, 86% of rural and 69% of urban preschool children have experienced dental caries, most of which remain untreated [1]. The dental treatment cost in young children is high due to the need for treatment under general anesthesia or sedation, therefore causing significant economic and social burdens on the families [2,3]. In 2012, nearly 4000 children in Malaysia were referred to hospital pediatric dental services because of dental caries [4].

Recent research has reported the effectiveness of dental home visits (DHVs) in preventing the development of caries in young children. The American Academy of Pediatric Dentistry describes DHVs as an ongoing relationship between the dentist and their patient, providing all aspects of a preventive oral health care program in the presence of the parents at home [5,6]. This concept has been reported to result in a sustainable oral health behavioral change as the child is more likely to receive appropriate preventive and routine oral health care, thereby reducing the risk of preventable dental disease [7]. In addition, DHVs have the advantage of providing a personalized preventive intervention based on a child's needs [8].

A study reported in 2013 by Plonka et al showed that oral health education for children through home visits significantly reduced the rate of development of early childhood caries (ECC) compared to those who were contacted via telephone [9]. The results of this study showed the benefit of personal contact in home visits for delivery of oral health education, and this significantly reduced the number of children who developed ECC [9].

Other studies have investigated the cost-effectiveness of DHVs in caries prevention. One such example is a study which investigated the benefit-cost and cost-effectiveness of a long term dental health program for prevention of ECC in infants through home visits, and this study showed favorable results [10]. In a separate study, a home-visit intervention for ECC was found to be more cost-effective than a telephone intervention delivery mode, contributing significant cost savings to the public health care system [11].

Educational leaflets (ELs) are one of the materials commonly used in oral health promotion programs, which reinforce oral health education messages and are frequently used for the benefit of dental patients to complement communication with the dentist [12,13].

Cost-effectiveness analysis (CEA) is widely used to inform decision-makers about the value of new health programs and interventions. CEA is the most commonly used technique for economic evaluation and it estimates the costs and effects of health interventions and sums up the results in a cost-effectiveness ratio [14].

Given the high prevalence of dental caries in Malaysia, and the availability of effective DHVs and ELs material to support oral health promotion, the rationale of this study is to identify effective and cost-effective behavioral interventions to promote oral health and reduce oral health disparities in the population [1,7,8,12,13]. Health behaviors and lifestyles can influence both

the oral and general long-term health of the population which can have economic and social consequences [15]. Furthermore, this is the first reported study of DHVs in Malaysia and an economic evaluation in this area is needed to estimate the value of the outcomes received for the expenditures spent on this intervention.

The aim of this study is to evaluate the cost-effectiveness of DHVs and oral health information in the form of ELs in preventing new caries development in young children, compared to those receiving only ELs over a period of 2 years. The specific objectives are:

1. To determine the cost of DHVs and ELs for prevention of new caries per child compared to the cost for a child only receiving oral health information through ELs for prevention of new caries after a 2-year follow-up.
2. To determine the cost of DHVs and ELs in improving the oral health-related quality of life (OHRQoL) for one child compared to the cost of only ELs in improving the OHRQoL for one child after a 2-year follow-up.
3. To compare the cost of dental treatment incurred and all associated expenditures among children receiving DHVs and ELs and those receiving only ELs over 2 years.

Methods

Study Design

This is a CEA of DHVs to families of young children for caries prevention compared to young children receiving oral health information in the form of ELs over a period of two years. For the CEA, the study adopted a societal perspective, which has been suggested as the most appropriate and comprehensive perspective [14]. In this perspective, all types of resources that are of value to society will be included in analyzing the costs; such as cost to the patient, cost to the provider or institution, and indirect costs because of loss of productivity.

Ethics, Consent, and Permission

Ethics approval for this project will be obtained from the International Medical University Malaysia's Joint Research and Ethics Committee. Approval for cooperation from the selected kindergartens will be obtained from the Ministry of Education of Malaysia.

Recruitment

This is a collaborative project with the Oral Health Division (OHD) of the Ministry of Health Malaysia. The OHD will provide access to a subsample population from the National Oral Health of Preschoolers Survey (NOHPS) which was carried out in 2015. The population of interest is children aged 5 and 6 years from kindergartens in the Selangor state in Malaysia. The names and addresses of the kindergartens will be obtained from the OHD.

Upon obtaining an appointment, the researchers will visit the selected kindergartens to provide details about project to the heads of the kindergartens and determine their interest in participating in the study. The heads will be asked to distribute the information leaflets and consent forms to all 5- and 6-year old children in the kindergarten to be taken home to their

parents. The information leaflet will include details about the study as well as the researchers' names and telephone numbers for any further enquiries. Parents will be given a week to read the information leaflet and to allow parents time to make any enquiries necessary before giving consent. The parents who agree to participate in the study will be asked to sign the consent form and provide their phone numbers, addresses, and children's names for future contact. The forms will be returned to the kindergarten. Participants in this study will be identified from the consenting families and only children aged 5 or 6 years at commencement of the study will be eligible for inclusion.

Sample Size and Randomization

It is estimated that there will be a 5% of incidence of caries in the intervention group during the follow-up, compared with 20% in the control group. This is based on the findings of a study conducted in 2015 by Koh et al that reported a 4% of incidence of caries in the intervention group and 39% in the control group [11]. Using a statistical software, Epi info 7 (Center for Disease Control and Prevention, USA, 2015), a sample size calculation was conducted and a minimum sample of 176 subjects is needed to detect a 15% difference in incidence of caries, with a significance level of 95% and a power of 80% [16]. The researchers decided to aim for doubling the effective sample size to 300 subjects to ensure the effective sample size will be higher than 176 with a high power. After taking sampling error into account and the assumption of a 30% nonresponse rate, followed by the assumption of another 30% of drop-out rate, a total of 600 subjects will be approached to participate in this study.

The kindergartens that agreed to participate will be randomly allocated into either the intervention or control group (1:1) by a random "draw" method. No matching will be done since they all have a similar socioeconomic background. All children aged 5 or 6 years at the participating kindergartens, with parents' consent to participate, will be included in the study [17].

The Intervention

All consenting families in the intervention group will receive DHVs and ELs delivering dental care advice by a team of two dental home visitors at 6-month intervals. This advice will include information regarding daily tooth brushing, simple diet advice to prevent caries, and information on the need for regular dental check-ups. The families will also be provided with information about the dental services available in their vicinity and how to access these services. The duration of each visit will be approximately 30 minutes. A personalized approach that avoids direct persuasion will be used, and the dental team will acknowledge the parents' right to choose when providing feedback and advice about dental care [18].

Control Group

The control group will receive ELs that will be delivered by hand at 6-month intervals for the 2-year study period by the dental home visitors.

Study Measures

Outcome Measures

The primary outcome of this study is the incidence of new caries, measured by the number of children included in the study with new caries, over a period of 2 years. The difference in the number of children with new caries between the intervention and the control groups will be considered as the number of children prevented from developing caries.

The calculated cost of the DHVs used in the intervention will include staff salaries, telephone calls to make appointments, travelling allowances, and administrative costs. The ELs cost is estimated by using the market price to purchase leaflets, staff salaries, telephone calls, travelling allowances, and administration costs. The cost of preventing a child from developing caries will be calculated as the DHVs and ELs cost divided by the number of children prevented from new caries.

The secondary outcome of this study will be the improvement in OHRQoL over a period of 2 years. This is measured by the improvement in the early childhood oral health impact scale (ECOHIS) scores. The difference in the ECOHIS scores between the intervention and the control groups will be considered as the improvement in OHRQoL. The cost of improving the OHRQoL is calculated as the DHVs and ELs cost divided by the improvement in the ECOHIS scores.

Number of New Carious Teeth

An oral examination will be conducted at baseline (before the start of the intervention) and at the end of the 2-year study period by researchers using the NOHPS protocol, which was based on the World Health Organization (WHO) recommendation published in 2013 [19]. The number of new decayed, missing (due to caries), and filled posterior deciduous teeth (dmft), as well as the number of decayed, missing (due to caries), and filled first permanent molars (DMFT) will be recorded. The dmft and DMFT caries assessment is chosen to ensure consistency with the assessment used by the OHD Ministry of Health Malaysia.

Oral Health-Related Quality of Life Improvement

The OHRQoL improvement will be measured using the ECOHIS questionnaire. The ECOHIS questionnaire is a specific instrument developed by Pahel et al in 2007 to assess the perception of parents on OHRQoL of preschool children. It has 13 items, distributed between 2 sections, namely the Child Impact Section and the Family Impact Section. The Child Impact Section has 4 domains (child symptom, function, psychological, and self-image or social interaction); and the Family Impact Section has 2 domains (parent distress and family function). Responses are recorded using a 5-point Likert scale to record how often an event has occurred where 0=never, 1=hardly ever, 2=occasionally, 3=often, 4=very often, and 5=don't know [20]. The ECOHIS has been validated on a Malaysian population and was found to have high validity (Cronbach alpha=.83) and high reliability (kappa=.95) in assessing the impact of oral disorders or conditions on the quality of life of urban preschool children age 4 to 6 years old as reported by Hashim et al [21].

The ECOHIS questionnaire will be completed by the parents in both the intervention and control groups at baseline and at the end of the 2-year follow-up period. Based on the responses, the ECHOIS score as prescribed by Hashim will be computed. The ECOHIS score at the end of the 2-year follow-up will be used to assess the improvement of OHRQoL of the children in both intervention and control groups.

Costs of Dental Home Visits and Educational Leaflets

The DHVs cost data will include the cost of dental home visitors, telephone calls, administration costs, and travelling costs of dental home visitors. The costs of the dental home visitors will be calculated according to the average salary of a dental nurse; the costs of the telephone calls used to make appointments for DHVs will be estimated according to the fees of prepaid phone number; and the travelling costs of the dental home visitors will be estimated by the average travel allowance per day in the Selangor area. The administration cost will include the costs of paper, stationary, and photocopies used for the informed consent forms and letters to authorities, as well as the training cost for delivering intervention. As the ELs used in the study will be obtained from existing Ministry of Health leaflets which are most relevant to the study objectives, the ELs cost in this study will be estimated by using the market price for purchase of leaflets, staff salaries, telephone calls, travelling allowances, and administration costs.

Costs of Dental Treatment

The cost data for dental treatment incurred by the families will be obtained from the recorded dental visit diary completed by the parents. The dental visit diary will be created to record every dental visit made during the study period and checked by the researchers every six months until the end of the study period. The information recorded in the diary will capture the reason for the dental visit, the type of dental clinic visited, the dental treatment or procedure conducted, the time spent at the dental clinic, the time spent travelling to and from the dental clinic, the total cost of the dental treatment or procedure, the cost of travelling to and from the dental clinic, the person who brought the child to the dental clinic, and the number of parents' days off used to bring the child to the dental clinic. The use of dental visit diary has been reported to be suitable for self-completion by the parents [22].

The dental visit diary will be created according to an annotated cost questionnaire as proposed and validated by Thompson and Wordsworth for the UK Health Economics Research Unit [22]. It will be translated to Bahasa Malaysia using the forward and backward translation process. It will be pretested to assess its relevance and ease of understanding by the potential participants in the context of the communities included in the study.

Data Collection Procedure

Standardization

Standardization and calibration training will be carried out by the OHD Ministry of Health Malaysia for the researchers in this project to ensure the reliability of the measurements in oral examination at the baseline and at the end of the 2-year

follow-up period. The training is carried out in order to achieve the following outcomes:

1. Uniform interpretation, understanding, and application of recording instructions and criteria.
2. Standardization and calibration of chosen examiners (researchers) against the benchmark examiner (OHD personnel).
3. Reasonable consistency with minimal inter- and intraexaminer variability.
4. Familiarization with survey forms, field procedures, and equipment to be used [23].

Baseline Data

The baseline clinical data for all study participants will be based on the oral examination to be carried out at the kindergarten for all children with the parents' consent. This examination will be conducted by researchers who have successfully attended the standardization training session. Oral examination will use a disposable mouth mirror. Caries assessment will be based on visual inspection, without invasive probing, and is diagnosed at the cavitation stage. Both primary and permanent teeth will be examined and if a permanent and a primary tooth occupy the same space, then only the status of the permanent tooth will be recorded. Caries assessment will adhere closely to the NOHPS criteria [17], which has been modified in 2013 from the WHO recommendations [21]. It is important to note that the WHO uses alphabets to denote caries status for primary teeth, however, NOHPS protocol uses numeral for both primary and permanent teeth. Hence, in this study, the following coding will be used: Sound teeth=0 (instead of A), Caries=1 (instead of B), Filled with caries=2 (instead of C) and Filled no caries=3 (instead of D). The teeth examination will begin from upper right to upper left and lower left to lower right quadrant and a tooth will be considered present when any part of it is visible [19,23]. No radiographs will be taken, and no treatment will be provided. Children who have been assessed with obvious caries will be advised to visit a dental clinic for further assessment and for treatment if necessary.

Baseline DHVs will be carried out and the parents in both the intervention and control groups will receive the ECOHIS questionnaire and a dental visit diary. The baseline ECOHIS questionnaire will be filled by the parents during the visit and returned to the researchers. The dental visit diary will be maintained by the parents and the research team will check the diary every 6 months. Parents will be informed to complete the diary every time their children visit the dental clinic.

Follow-Up 6-Monthly Visits

Follow-up visits will be made every 6 months at the 6th, 12th, 18th month of the study period to the homes of both the groups. The parents in intervention group will receive DHVs and ELs by the dental home visitors, while those in the control group will receive only ELs to be delivered by the dental home visitors. The researchers will check the dental visit diary from both groups at each 6-month visit.

The 2-Year Follow-Up Data

At the end of the 2-year study period, the researchers will visit the subjects' homes from both the intervention and control groups and repeat the same dental examination, complete the ECOHIS questionnaire, and gather the information from the dental visit diary. At the 2-year follow-up visit, the subjects will be 7 or 8 years old. It is anticipated that, should new caries develop, the majority will be on primary posterior teeth and first permanent molars. Adhering to the NOHPS protocol, the follow-up oral examination will be carried out to collect the number of new decayed, missing (due to caries) and filled posterior deciduous teeth (dmft), and the number of decayed, missing (due to caries) and filled first permanent molars (DMFT). The children will be examined while sitting on a portable dental chair at their homes. The visual oral examination will use disposable mouth mirrors with natural daylight for illumination, supported by a Daray lamp where necessary. No radiographs will be taken, and no treatment will be provided. Children who have been assessed with obvious caries will be advised to visit a dental clinic for further assessment and treatment if necessary. The researcher will offer to provide information or make the necessary arrangements for families who wish to have further assessment at a dental clinic.

Data Analysis

Data collected from each visit will be checked for completeness by the research team members before it is keyed into SPSS. All the outcomes measures will be analyzed using the SPSS Program. Descriptive statistics will be used to report new caries teeth, OHRQoL, cost of DHVs and ELs, and the incremental cost effectiveness ratio (ICER) at 6, 12, and 18 months, as well as at the end of the 2-year follow-up period. A *t* test will be used for comparison of means of those parameters between the two groups and over the period of study. Logistic regression analysis will be carried out to test the influence of individual characteristics and on the CEA of the intervention in preventing caries.

Cost-Effectiveness Analysis

The CEA will measure cost in monetary units of DHVs and ELs. The effectiveness of the study is measure by the outcomes

in number of teeth saved and the ECOHIS score at the 2-year follow-up. CEA assesses the cost of the study through the use of the ICER [8,24,25] and is defined as the ratio of the difference in costs divided by the difference in outcomes. The ICER for this study will be generated by calculating the difference in cost for dental treatment between the intervention group and the control group, divided by the difference in outcomes between the intervention group and the control group (ie, the number of new carious teeth and ECOHIS scores) [8,24,25]. Based on the data collected, the outcome measure for OHRQoL is only from the ECOHIS questionnaire, therefore this study focuses on CEA as a procedure to decide the most cost-effective way to achieve the objectives [11]. Discounting and sensitivity analysis are not conducted because the study does not perform any projection of future years and the cost data of this study is the real-world cost data [14].

Results

The trial has been approved by the International Medical University Malaysia's Joint Research and Ethics Committee (Project ID: IMU R157-2014 [File III – 2016]). Participants are currently being recruited for inclusion in the study.

Discussion

The cost of dental treatment in young children is high due to the severity of the caries developed which can require an aggressive treatment, as well as the need for general anesthesia or sedation. Children who receive treatment under general anesthesia frequently require further hospitalization for new lesions, some as soon as 6 months after the first general anesthesia. Clearly, existing health services need to be supplemented with a population-based approach to promote child oral health. This is the first study of this intervention in Malaysia, and economic evaluation in this area is crucial to estimate the value of the outcomes received for the expenditures spent on this intervention. This study will provide information on the cost and effectiveness of DHVs in caries prevention of young children in Malaysia.

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Conflicts of Interest

None declared.

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Abbreviations

CEA: cost-effectiveness analysis
dfmt: decayed, missing (due to caries), and filled posterior deciduous teeth
DFMT: decayed, missing (due to caries), and filled first permanent molars
DHV: dental home visit
ECC: early childhood caries
ECOHIS: early childhood oral health impact scale
EL: educational leaflet
ICER: incremental cost-effectiveness ratio
NOHPS: National Oral Health of Preschoolers Survey
OHD: Oral Health Division
OHRQoL: oral health-related quality of life
WHO: World Health Organization

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Protocol

An Integrated Approach to Control Soil-Transmitted Helminthiasis, Schistosomiasis, Intestinal Protozoa Infection, and Diarrhea: Protocol for a Cluster Randomized Trial

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Abstract

Background: The global strategy to control helminthiasis (schistosomiasis and soil-transmitted helminthiasis) emphasizes preventive chemotherapy. However, in the absence of access to clean water, improved sanitation, and adequate hygiene, reinfection after treatment can occur rapidly. Integrated approaches might be necessary to sustain the benefits of preventive chemotherapy and make progress toward interruption of helminthiasis transmission.

Objective: The aim of this study was to assess and quantify the effect of an integrated control package that consists of preventive chemotherapy, community-led total sanitation, and health education on soil-transmitted helminthiasis, schistosomiasis, intestinal protozoa infection, and diarrhea in rural Côte d'Ivoire.

Methods: In a first step, a community health education program was developed that includes an animated cartoon to promote improved hygiene and health targeting school-aged children, coupled with a health education theater for the entire community. In a second step, a cluster randomized trial was implemented in 56 communities of south-central Côte d'Ivoire with 4 intervention arms: (1) preventive chemotherapy; (2) preventive chemotherapy plus community-led total sanitation; (3) preventive chemotherapy plus health education; and (4) all 3 interventions combined. Before implementation of the aforementioned interventions, a baseline parasitologic, anthropometric, and hygiene-related knowledge, attitudes, practices, and beliefs survey was conducted. These surveys were repeated 18 and 39 months after the baseline cross-sectional survey to determine the effect of different interventions on helminth and intestinal protozoa infection, nutritional indicators, and knowledge, attitudes, practices, and beliefs. Monitoring of diarrhea was done over a 24-month period at 2-week intervals, starting right after the baseline survey.

Results: Key results from this cluster randomized trial will shed light on the effect of integrated approaches consisting of preventive chemotherapy, community-led total sanitation, and health education against infections with soil-transmitted helminths, schistosomes, an intestinal protozoa and prevention of diarrhea in a rural part of Côte d'Ivoire.

Conclusions: The research provided new insights into the acceptability, strengths, and limitations of an integrated community-based control package targeting helminthiasis, intestinal protozoa infections, and diarrhea in rural communities of Côte d'Ivoire. In the longer term, the study will allow determining the effect of the integrated control approach on infection patterns with parasitic worms and intestinal protozoa, diarrheal incidence, anthropometric measures, and hygiene-related knowledge, attitudes, practices, and beliefs.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 53102033; <http://www.isrctn.com/ISRCTN53102033> (Archived by WebCite at <http://www.webcitation.org/6wpmXEiHo>)

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KEYWORDS

community-led total sanitation; Côte d'Ivoire; diarrhea; health education; integrated control; intestinal protozoa; preventive chemotherapy; schistosomiasis; soil-transmitted helminthiasis

Introduction

The global strategy to control helminthiasis (eg, schistosomiasis and soil-transmitted helminthiasis) emphasizes preventive chemotherapy, that is, the periodic administration of anthelmintic drugs to at-risk populations, most importantly school-aged children [1]. However, preventive chemotherapy does not prevent people from rapid reinfection with parasitic worms [2,3]. In view of the current discussion and efforts to shift from morbidity control to interruption of transmission of helminthiasis and other neglected tropical diseases, ongoing efforts need to be intensified, along with concurrent implementation of complementary interventions [4-7]. Indeed, integrated approaches, combining preventive chemotherapy with water, sanitation, and hygiene and information, education, and communication, are necessary to sustain the gains made in the control of helminthiasis and eventually break transmission [8-11].

In 2015, an estimated 2.4 billion people globally lacked access to improved sanitation, and the absolute number of people practicing open defecation in Africa had increased since 1990 [12]. There is evidence that a considerable part of the global burden of disease is attributable to unsafe sanitation, poor water quality, and inadequate hygiene behavior [13,14] and that improved sanitation and water supply are key factors for prevention, control, and elimination of helminthiasis and diarrhea [11,15-18]. Yet, current control efforts do not take these aspects sufficiently into account. Combined interventions have shown around 35% reduction in the incidence of diarrheal diseases and helminthiasis [15,19,20] with improved sanitation being particularly important [21]. Studies pertaining to the effect of improved sanitation combined with preventive chemotherapy suggest reductions of 75% and up to 90% for each of the 3 common soil-transmitted helminth species (*Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) [22,23]. Hence, sanitation and specific health education protect people from rapid reinfection, consolidate the gains of preventive chemotherapy, and are crucial for the sustainability of control programs [24-26].

In 2013, a project was launched in south-central Côte d'Ivoire with the aim to assess and quantify the effect of preventive chemotherapy, combined with either community-led total sanitation (CLTS), or health education, or both measures combined, on reinfection with soil-transmitted helminths, schistosomes, intestinal protozoa, and the incidence of diarrhea, using a cluster randomized design. CLTS was initially designed to reduce diarrhea incidence; through a participatory grassroots approach, it aims to achieve and sustain an open defecation-free status of the target community [27].

In a first step, we developed a community health education program (CHEP), including an animated cartoon entitled *Koko et les lunettes magiques* for school-aged children [28] and a health education theater targeting the entire community. The emphasis of these health education tools is placed on improving people's hygiene behavior to prevent the transmission of neglected tropical diseases and diarrhea. In a second step, a cluster randomized trial was implemented in 56 communities of the Taabo, Djékanou, and Toumodi departments in south-central Côte d'Ivoire. Here, we present the study protocol with particular consideration to the cluster randomized trial, whose aim was to assess the effect of preventive chemotherapy combined with either CLTS or CHEP, or both on infections with soil-transmitted helminths, schistosomes, and intestinal protozoa.

Methods

Ethics Approval and Consent to Participate

Ethical clearance for the study was obtained from the Ethics Committee of Basel (EKBB; reference no. 300/13, date of approval: November 11, 2013) and from the ethics committee of the Ministry of Health and Public Hygiene in Côte d'Ivoire (reference no. 76-MSLS-CNER-dkn, date of approval: November 28, 2013). The trial is registered (ISRCTN53102033, date of approval: March 26, 2014). Written informed consent was obtained from each participant, with parents/guardians consenting on behalf of children younger than 18 years.

Study Area and Participants

Between July 2011 and December 2012, an 18-month pilot project, entailing a baseline parasitologic and knowledge, attitudes, practices, and beliefs (KAPB) cross-sectional survey, followed by a cross-sectional follow-up survey, was carried out to study the effect of an integrated disease control package, consisting of preventive chemotherapy, CLTS, and health education against helminthiasis and intestinal protozoa infections in 9 communities of the Taabo health and demographic surveillance system in south-central Côte d'Ivoire [29-32]. The results of this pilot project provided an indication that an integrated control package reduced the prevalence of helminth and intestinal protozoa infections and improved people's hygiene knowledge and practice. In addition, the study results suggested that health education is an important complement, as it enhanced CLTS acceptance in the community [33].

Following this pilot project, a larger study was launched in 2013 to assess the effect of an integrated control package in a community cluster randomized trial with 4 intervention arms (preventive chemotherapy alone, or combined with either CLTS or CHEP, or both interventions simultaneously). This trial was implemented in 56 rural communities in 3 departments of south-central Côte d'Ivoire; namely, Taabo, Djékanou, and Toumodi. In this part of Côte d'Ivoire, people are mainly engaged in subsistence agriculture, whereas rubber, cocoa, and coffee are farmed as cash crops.

Development and Validation of Health Education Tools

Before starting the cluster randomized trial in the 3 departments, 2 types of health education tools were developed, refined, and tested—an animated cartoon entitled *Koko et les lunettes magiques* [28] and a community-based health theater. For the development of the animated cartoon, a formative research was conducted with school-aged children to identify key messages to improve hygiene behavior and to prevent transmission of neglected tropical diseases that were subsequently included in the video. The research was done with school-enrolled and nonenrolled children in 8 localities in south-central and western Côte d'Ivoire, in the same regions where further studies would take place [28]. Hence, the 8 localities were excluded from further research. The animated cartoon was produced by an Abidjan-based cartoon company, in collaboration with the research team, and was tested for comprehension and acceptance with school children. Subsequently, the cartoon was validated, and its effect on helminth infections and KAPB was determined in an intervention study comprising 25 schools of western Côte d'Ivoire from 2014 to 2015. This intervention study confirmed that knowledge of school children was improved after screening the cartoon, and hence, the cartoon was deemed a useful tool for health education. However, no significant effects on helminth infections were observed in the short term.

As for the development of the animated cartoon, the health education theater was coupled to a KAPB survey in the community. Questionnaires and focus group discussions (FGDs) were administered to groups of women, men, young adults, and the elderly in 2 communities of the nearby Tiassalé department. In addition, direct observations were made with an emphasis

on hygiene behavior and transmission of neglected tropical diseases. Community members constituted a theater group that was assisted by the research team who provided a health education session, according to KAPB survey results. The community theater members designed the sketches on their own and conveyed hygiene and health messages during their performance in front of the community. The health education theater was tested with 2 communities and then evaluated for its acceptance in the community in 2014. For this purpose, the team discussed with the community their opinion about the intervention, whether they liked it, if they thought it was helpful to improve their health knowledge, and whether they would welcome such kind of interventions. Figure 1 summarizes the 3-step methodological approach for the development of health education tools, comprising identification of key messages, development, and refinement of the tool.

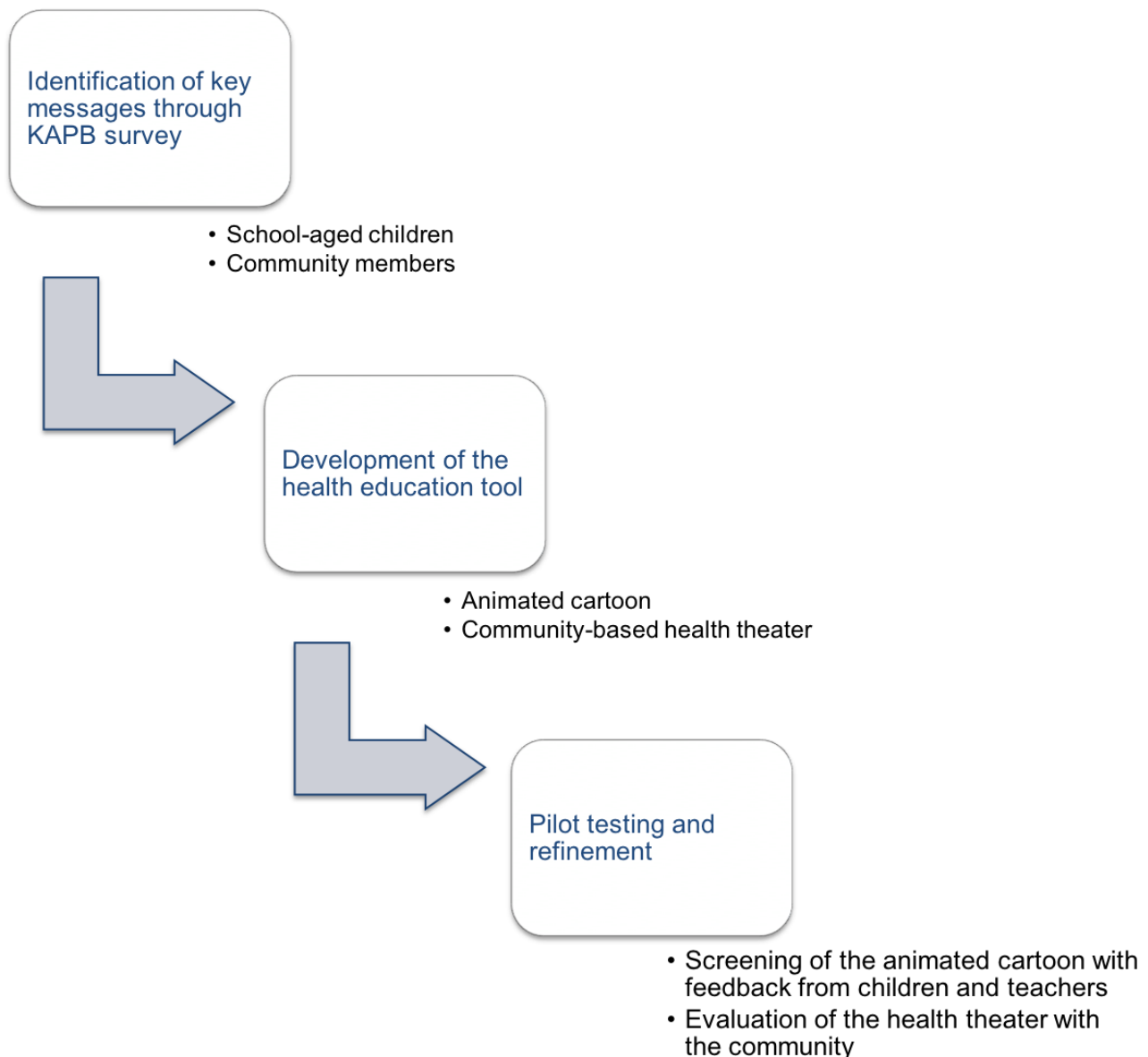
Cluster Randomized Trial Design

Once the health education tools had been developed and validated, a 4-armed cluster randomized trial was launched. The primary outcome of the trial was hookworm infection, as determined by the Kato-Katz method [34]. Secondary outcomes were other parasitic infections (ie, other soil-transmitted helminths, *Schistosoma* spp., and intestinal protozoa) and intensity of helminth infection, KAPB with regard to hygiene and intestinal parasitic infections, diarrhea incidence, and anthropometry of infants. Hookworm infection was chosen as primary outcome because of its endemicity across Côte d'Ivoire and the moderate to high prevalence in the study area [33,35].

Details of the specific outcomes are provided in the following sections. In a first step, a baseline parasitologic, KAPB, and anthropometric survey was implemented in 56 communities (14 communities per arm). Sample size calculation was done using the Web-based sample calculator for cluster randomized trials presented elsewhere [36], assuming a baseline hookworm prevalence of 30% according to previous studies in the region [33,37], a prevalence reduction of 50% after implementation of interventions [33], an intracluster correlation of .4 as we expected high correlation within the community because of the nature of community-based bottom-up interventions and mass drug administration within a community, and a dropout rate of 30% at each follow-up according to previous experience of the team, resulting in 152 individuals per cluster. In Côte d'Ivoire, the average number of people in a household is 7 (our assumption was 2 adults and 5 children). For a sample size of 152 children per community, we thus needed 30 households per community.

The communities were selected based on their population size. We intended to include communities with at least 30 households and a population size not exceeding 600 individuals because this is the optimal recommended size for implementation of the CLTS intervention [27]. Given the demographic characteristics of the study area, somewhat smaller communities (slightly less than 30 households) and villages exceeding 600 individuals were also included. The selection of up to 30 households per community was done at random, according to the World Health Organization's (WHO) Expanded Program on Immunization method [38].

Figure 1. Proposed 3-step process for the development and testing of health education tools for the control of neglected tropical diseases. KAPB: knowledge, attitudes, practices, and beliefs.



Our main target group was children aged 5 to 15 years, on whom sample size calculation was based. In addition, whenever possible, 1 infant (aged 12-24 months) and 1 adolescent or adult (aged >15 years) from each household were also selected. Although all the 3 groups underwent parasitologic examinations, only infants were subjected to anthropometric measurements. Household heads (or their spouses/partners) were administered a questionnaire for KAPB, whereas direct observations occurred in each household to check for the presence, use, and maintenance of latrines as well as potential open defecation and waste disposal sites in close proximity. The questionnaire included a section reserved for these observations that were made by the interviewer during the interview. FGDs were conducted with selected groups (adult women, adult men, school-aged children, and the elderly), and in-depth interviews were conducted with head of communities and community health workers in 24 communities. The topics discussed during

the FGDs were the same as for the questionnaires so that qualitative and quantitative results complemented each other. We monitored diarrhea over a 24-month period, determining the length and frequency of each episode, using a rapid assessment questionnaire carried out once every 2 weeks. The trial communities were assigned by restricted randomization to 1 of the 4 intervention arms with 14 communities per intervention arm based on baseline soil-transmitted helminth prevalence and population size [39]. The 4 intervention arms are as follows: (1) intervention arm 1: preventive chemotherapy only; (2) intervention arm 2: preventive chemotherapy plus CLTS; (3) intervention arm 3: preventive chemotherapy plus health education; and (4) intervention arm 4: all interventions combined.

Figure 2 shows the study area with the 56 selected rural communities, stratified by intervention arm. Interventions started

right after randomization of the communities. A first follow-up parasitologic and KAPB survey was carried out 18 months after the baseline cross-sectional survey. A second follow-up survey was scheduled another 21 months later. At the end of the CLTS intervention, the communities were visited and inspected using

standardized forms. Transects were done to assess whether open defecation and waste disposal spots were visible, and all households were inspected for the availability of latrines. A summary of the study design is presented in [Figure 3](#).

Figure 2. Map displaying communities included in the cluster randomized trial in 3 departments of south-central Côte d'Ivoire randomly assigned to one of 4 intervention arms. PC: preventive chemotherapy; CLTS: community-led total sanitation; CHEP: community health education program.

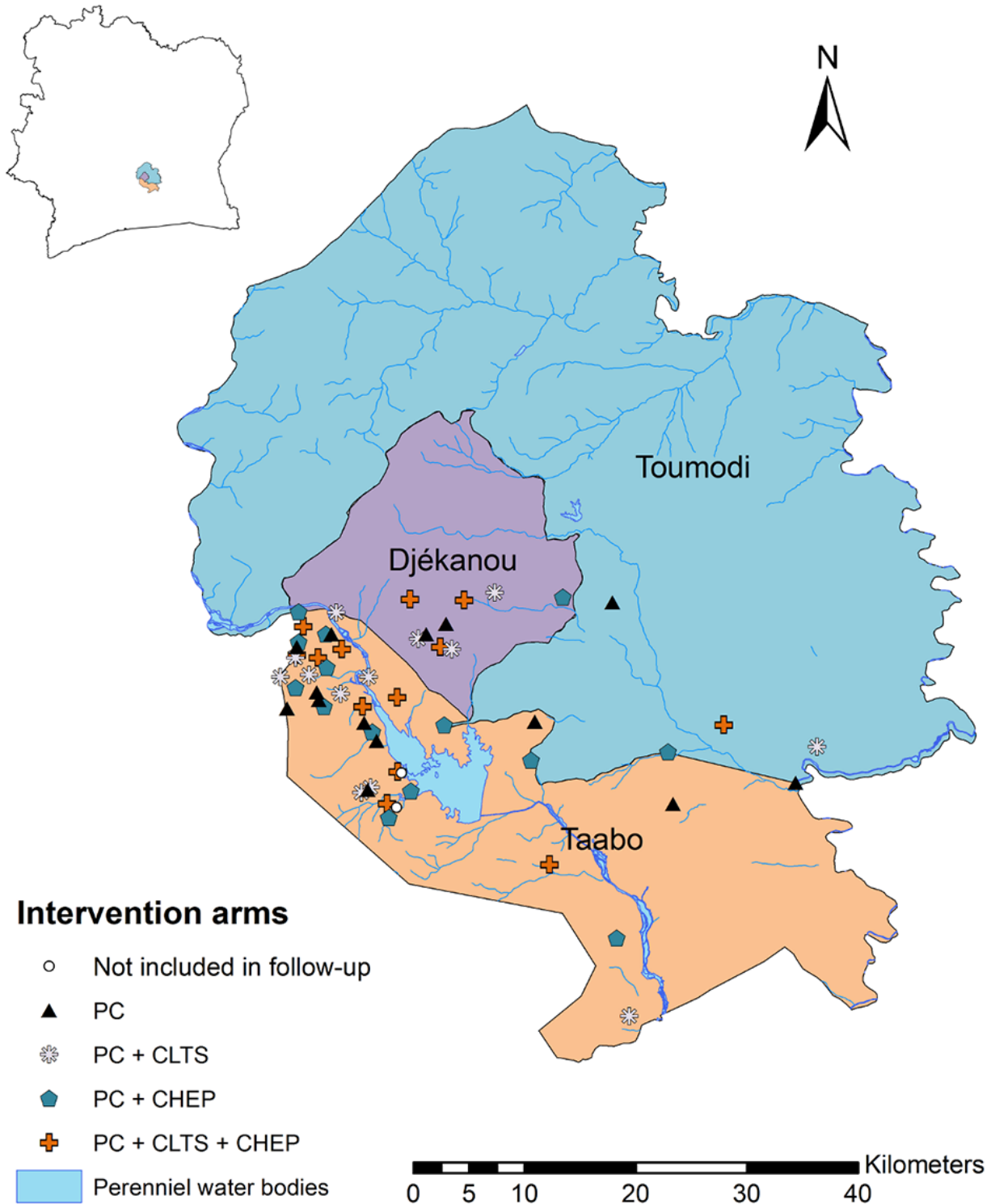
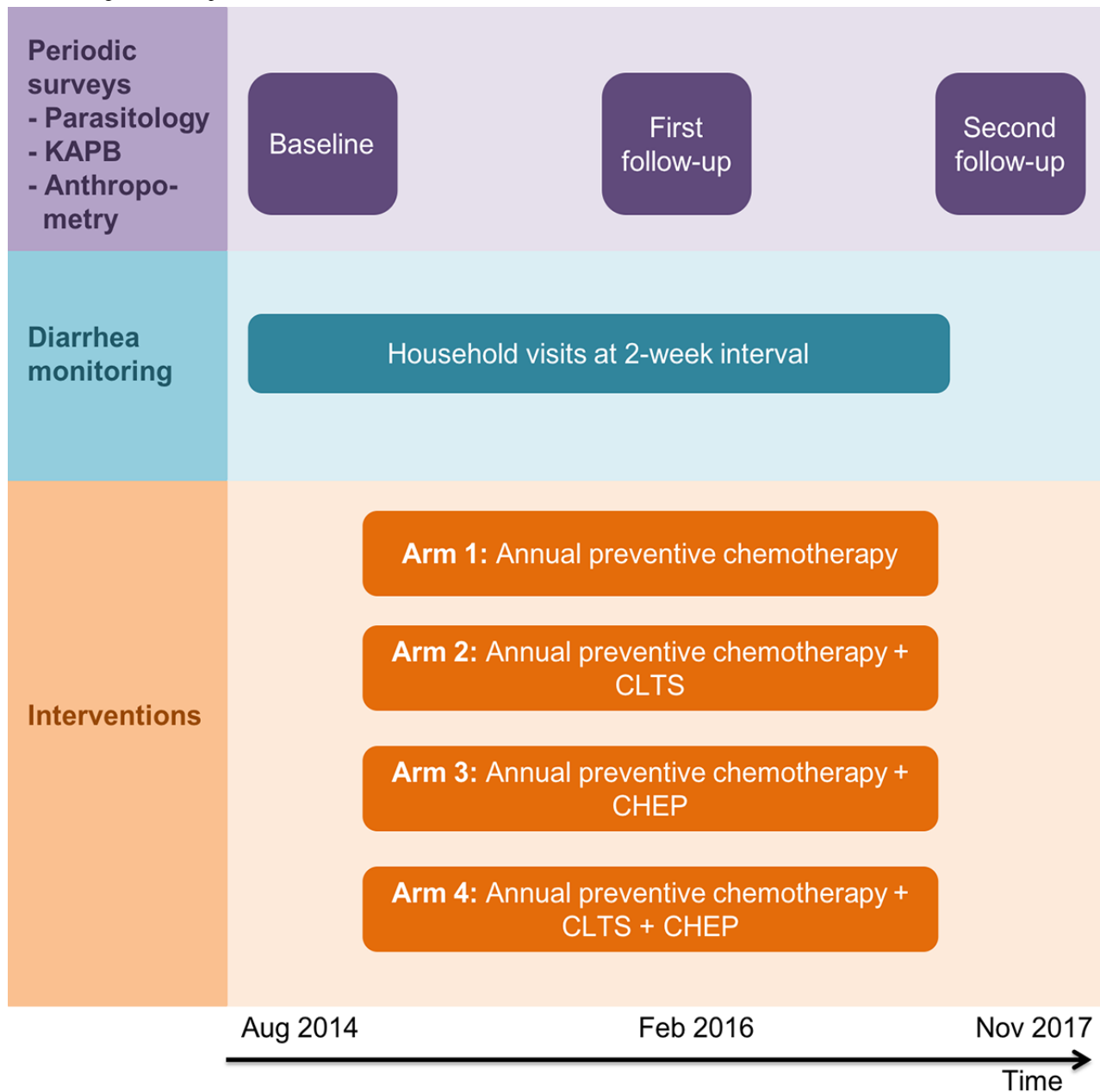


Figure 3. Experimental design of the cluster randomized trial. The periodic cross-sectional surveys are highlighted in purple color, diarrhea monitoring is marked in blue, and interventions are highlighted in orange. CLTS: community-led total sanitation; CHEP: community health education program; KAPB: knowledge, attitudes, practices, and beliefs.



Enrollment and Written Informed Consent

For the whole study, including the parasitologic survey, preventive chemotherapy, the KAPB survey, and the interventions (CLTS and CHEP), village authorities were contacted once ethical approval had been granted. The objectives, procedures, and potential risks and benefits were explained. Subsequently, the community was informed about the aims and procedures. A patient information sheet was administered to all participants, explaining objectives, procedures, and potential risks and benefits of the study. Names and contact address of the main investigators were readily provided on this information sheet so that investigators could be contacted anytime if need be. For illiterate participants, the information sheet was read aloud, and, if necessary, an oral translation of the information into a local language was provided

in the presence of a team member and a witness from the community. Written informed consent was obtained from each participant, with parents/guardians consenting on behalf of children (aged <18 years). It was emphasized that participation is voluntary, and hence, participants could withdraw from the study at any time without further obligation. Moreover, it was mentioned that preventive chemotherapy was provided to all people in the study area, not just those who decide to participate, free of charge through the national control program.

Inclusion and Exclusion Criteria

All household heads or their representatives of the selected households of the 56 communities were invited to participate in the questionnaire survey, and all children aged 5 to 15 years, 1 infant (aged 12-24 months), and 1 adolescent or adult (aged >15 years) from these households were invited for parasitologic

examination, unless they met any of the following exclusion criteria: (1) no written informed consent or no parental/guardian's permission to participate; and (2) too sick to participate in the study, as determined by qualified medical personnel. All members of the intervention communities were invited to participate in the implementation of CLTS and the CHEP sessions.

Cross-Sectional Surveys

Four teams were formed, each consisting of 1 driver, 2 laboratory technicians, 2 laboratory assistants, 3 field enumerators, 1 parasitologist/epidemiologist (team supervisor), and 1 social scientist. Each team was responsible for carrying out the cross-sectional parasitologic, anthropometric, and KAPB survey in their designated communities. The teams were based in 2 central laboratories of the study area, which are in close proximity to the survey locations. Moreover, 1 to 2 weeks before a cross-sectional survey, the study team visited the communities to announce the upcoming activities and to provide village authorities and inhabitants with exact dates and procedures of the survey.

Parasitologic Surveys

A day before the first sampling, the study team conducting the survey visited the selected households and distributed empty plastic containers for stool and urine collection. The team revisited the households to collect the samples early in the morning of the next day [40]. Stool and urine samples were transferred to laboratories at the general hospitals of Taabo and Djékanou, the community health center at Kpouèbo, or a mobile field laboratory set up at the dispensary of Léléblé.

Participants' infection status with helminths (*A. lumbricoides*, hookworm, *Schistosoma mansoni*, and *T. trichiura*), pathogenic intestinal protozoa (*Giardia intestinalis*, *Entamoeba histolytica*/*E. dispar*), as determined in stool samples, and *S. haematobium*, determined in urine samples, were recorded. From each stool sample, duplicate Kato-Katz thick smears were prepared, using a standard template holding 41.7 mg of feces [34]. The slides were allowed to clear for 30 to 45 min before examining under a microscope by experienced laboratory technicians. Helminth eggs were counted and recorded for each species separately. For quality control, approximately 10% of the slides, selected at random, were reexamined by a senior laboratory technician [41]. Urine samples were examined for microhematuria using reagent strips (Hemastix; Siemens Healthcare Diagnostics GmbH, Eschborn, Germany). A subsample of 10% of urine specimens was subjected to a filtration method for evaluation of the reagent strip results. Ten milliliters of vigorously shaken urine were pressed through a membrane (diameter: 13 mm; pore size: 30 µm; Sefar AG, Heiden, Switzerland) and the membrane placed on a microscope slide. A drop of Lugol's iodine was added on the slide, and the number of *S. haematobium* eggs was counted under a microscope by experienced laboratory technicians [42].

In addition, 1 to 2 g of stool from each specimen was transferred into small tubes, filled with 10 mL of sodium acetate-acetic acid-formalin (SAF) for subsequent diagnosis of intestinal protozoa. In short, the SAF-fixed stool samples were forwarded

to a laboratory at the Université Félix Houphouët-Boigny in Abidjan and subjected to an ether-concentration method and examined under a microscope by experienced laboratory technicians. We adhered to a standard protocol [43].

Anthropometric Measurements

In intervention arms 1 and 4, infants aged 12 to 24 months were assessed for standard anthropometric measures, including weight (to the nearest 0.1 kg; mothers holding their infant were weighed with a portable scale, and then the weight of the mother was subtracted to obtain the weight of the infant) and height (measured to the nearest cm using a portable centimeter scale). Nutritional status of children at baseline and follow-up was evaluated using the following indicators: underweight (weight for age), stunting (height for age), and wasting (weight for height).

Knowledge, Attitudes, Practices, and Beliefs Surveys

People's KAPB were assessed, using a combination of direct observations and interviews (questionnaire surveys, in-depth interviews, and FGDs). All the components of the KAPB study were conducted in parallel to the baseline and follow-up parasitologic and anthropometric surveys.

The main topics that were investigated in the KAPB survey pertained to perceived needs of sanitation facilities, common defecation practices, availability and use of latrines, associations of defecation and hygiene behavior (eg, washing hands), general knowledge of health risks associated with (open) defecation, signs and symptoms of parasite infections, and how such infections can be prevented and treated [24]. Direct observations and questionnaires were addressed to household heads or their representatives at the unit of the household in the 56 communities. Questionnaires were designed in a semistructured manner with mainly closed but also a few open-ended questions to gather quantitative and qualitative data for the analyses. All interviews were conducted by trained field enumerators in French or local languages. Before the start of the survey, the questionnaire and the direct observation checklist were pretested in neighboring communities that were not part of the study, as done in previous research [44,45].

FGDs were conducted with different groups; namely (1) adult women; (2) adult men; (3) school-aged children; and (4) the elderly. FGDs were conducted in 8 villages; 2 villages per intervention arm. In each FGD, 8 to 10 individuals were invited to participate [46]. FGDs were tape-recorded for subsequent transcription and analysis. In-depth interviews were conducted with community health workers and traditional healers in the same 8 villages.

Diarrhea Monitoring

We monitored the incidence of diarrhea (duration and severity) over a 24-month period. Every second week, a short questionnaire was administered by community health workers to all members of the 30 selected households per community, starting right after the baseline cross-sectional survey. For the youngest children who were not able to answer the questionnaire, their mothers/caregivers were interviewed.

Implementation of Interventions

The interventions were implemented after the baseline cross-sectional survey. The CLTS intervention was started in the communities of intervention arms 2 and 4. Only after these communities had commenced building latrines, the CHEP was launched in the communities of intervention arms 3 and 4 to avoid interference with the methodological approach of the CLTS intervention (see section Community-Led Total Sanitation) in arm 4. Preventive chemotherapy was done according to ongoing activities of the national helminthiasis control program of the Ministry of Health in Côte d'Ivoire. These activities consist of community-based yearly mass administration of ivermectin and albendazole (against lymphatic filariasis) and yearly administration of praziquantel and albendazole (against schistosomiasis and soil-transmitted helminthiasis) to at-risk groups, adhering to WHO guidelines [47].

Preventive Chemotherapy

After the baseline cross-sectional survey, in October 2014, all participants found positive for *S. mansoni*, or *S. haematobium*, or both, received a single 40 mg/kg oral dose of praziquantel using a dose pole for individuals aged 4 years and older, whereas albendazole (single 400 mg dose for participants aged >2 years and 200 mg for 1- to 2-years-old children) was administered against soil-transmitted helminths [48]. Thereafter, annual preventive chemotherapy was administered in the frame of the on-going helminthiasis control activities by the Ministry of Health in Côte d'Ivoire. Annual preventive chemotherapy against lymphatic filariasis was done between May and June and against schistosomiasis between October and November. Participants with persistent diarrhea identified during the diarrhea monitoring received oral rehydration solutions and, if needed, were referred to nearby health facilities.

Community-Led Total Sanitation

The CLTS approach is based on participatory rural appraisal that emphasizes that the learning effect is considerably higher if knowledge is acquired through self-experience and self-reflexion. It facilitates critical analysis by the community of their own sanitation profile, their practices of defecation, and the consequences, leading to collective action to become open defecation-free [49,50]. The approach thus focuses on the whole community and their cooperation and interactions because the community only profits when every single community member cooperates and takes action [51]. CLTS is a grassroots, community-based, and community-led strategy that triggers community empowerment via feelings of shame and disgust induced through observation of the defecation situation in a specific setting and its environment, which is often missed by health education [52,53].

Before the intervention, CLTS facilitators were trained and instructed during a 1-week workshop by certified national CLTS facilitators from the Ministry of Sanitation, UNICEF, and a Swiss-based nongovernmental organization (FAIRMED). Communities were contacted, and a first community meeting was organized. During this meeting, the ignition process of CLTS was started, which could include the following

components according to Kar and Chambers [27]: (1) transect walk ("walk of shame") through the open defecation areas and water points; (2) defecation map, mapping of defecation areas and defecation mobility; (3) identifying the dirtiest neighborhoods; (4) calculation of feces amount and medical expenses; and (5) triggering disgust pathways of fecal contamination (glass of water, feces to food exercise, flow diagrams of fecal-oral routes, etc). These components were used to initiate the ignition moment (we are eating each other's feces!). When talking about feces, the term "caca" was employed, as "caca" had been identified as the most suited and culturally accepted term by CLTS facilitators in Côte d'Ivoire. Subsequently, 2 more steps were pursued that include the identification of natural leaders and the monitoring and sustaining of open defecation-free status or the process toward an open defecation-free community. Although CLTS encourages the communities to build basic sanitary facilities (ie, latrines), to change one's hygiene behavior, and to alter people's waste disposal practices, it does not impose standard designs and does not provide subsidies. Hence, for toilet construction, most communities used readily available local material, so that toilets were more affordable and accessible for rural communities. When a given community decided to go toward open defecation-free status, an implementation plan of community-based basic sanitation and hygiene services was elaborated. This community was frequently visited by the community development agents to ensure that the implementation of the different actions was done according to protocol.

Community Health Education Program

Once communities were well advanced or staggered with the construction of latrines, they were visited by the research team, and a first health education session was offered for the entire community, based on results from the preceding FGDs that facilitated the social science team to identify knowledge gaps and related key health messages. In each community, interested community members (up to 10) were identified (mostly by the village chief and other village authorities) and invited to form a community health theater group. In a further visit, the community theater group received an additional health education session by the team and was coached to develop its own sketch to deliver hygiene and health messages in front of the community. In a final visit, the theater group presented the sketch to the community, and during this visit, the animated cartoon was screen played to children, although adults were also invited to watch. After the theater and screening of the cartoon, people were grouped into adult women, adult men, school-aged children, and the elderly, and discussions about health and hygiene topics were pursued to determine their understanding.

Statistical Analysis

Data collected from the parasitologic and anthropometric surveys and the monitoring of diarrheal episodes were double entered and cross-checked in EpiInfo version 3.5.3 (Centers for Disease Control and Prevention; Atlanta, GA, USA). Household questionnaire data and direct observations were entered on tablets, using open data kit, and uploaded on a server hosted at

the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland). Statistical analyses were done on STATA, version 14 (Stata Corp; College Station, TX, USA).

To receive a standard infection intensity measure of eggs per 1 g (EPG) of stool, helminth species-specific egg counts from the individual Kato-Katz thick smears were multiplied by a factor of 24. For each individual, the arithmetic mean egg count was estimated. The geometric mean of the helminth infection at the population level was calculated from the arithmetic means of the individual infection intensities. To assess the effect of the interventions, helminth egg count reductions were determined as $1 - (\text{geometric mean EPG after 1 year at follow-up} / \text{geometric mean EPG at baseline})$ multiplied by a factor 100 and compared between intervention groups.

The nutritional status for children aged <5 years was determined using available macros for STATA version 10.1 with child growth standards and references published by WHO [54] and means between intervention groups, compared between baseline and follow-up. The same approach was used for diarrheal episodes, whereas the prevalence is being defined as the percentage of days with diarrhea, calculated as the number of days with diarrhea divided by the total number of days of observation. Incidence is defined as the number of new episodes divided by the number of days at-risk, which is defined as the number of days of observation minus the number of days with diarrhea self-diagnosis, allowing for 2 illness-free days between episodes [55].

Random effect logistic regression models were used to assess the effect of interventions on infection, anthropometric, diarrhea, and KAPB outcomes, using a factorial design. Qualitative data gathered from the FGDs were transcribed and processed in MaxQDA 10/Atlas version 1 (VERBI Software Consult; Berlin, Germany). The coded data were analyzed for the frequency at which coded information and content categories occur. The most frequently occurring topics concerning the study population's KAPB were analyzed for change after the implementation of CLTS and/or CHEP.

Dissemination of Key Findings

Progress and key results of this cluster randomized trial were communicated at annual workshops with key decision makers and other stakeholders, including community members.

Results

The project was funded in May 2013 and enrollment was completed in September 2014. Baseline, follow-up I, and follow-up II surveys were completed in September 2014, February 2016, and November 2017, respectively. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018. The findings will be published in peer-reviewed literature and presented at national and international conferences.

Discussion

Neglected tropical diseases, including soil-transmitted helminthiasis, schistosomiasis, giardiasis, and amoebiasis, are

important public health issues in Côte d'Ivoire and elsewhere in low- and middle-income countries [14,56-58]. Indeed, a recent national school-based survey in 94 schools across Côte d'Ivoire revealed that 26% of children aged 5 to 15 years had a helminth infection [59]. Giardiasis and amoebiasis were reported from community- and school-based surveys in different parts of Côte d'Ivoire [30,60,61]. The aim of this project was to assess the effect of an integrated control package, consisting of preventive chemotherapy with either CLTS or CHEP, or all measures combined in 56 small rural communities of south-central Côte d'Ivoire, using a cluster randomized trial. The goal was to generate new evidence to determine whether an integrated control package, including community-based approaches, is useful for the control of helminth and intestinal protozoa infections and thus to assist decision making in translating global policy into local practice.

A previous pilot study in Côte d'Ivoire revealed that CLTS coupled with health education and preventive chemotherapy has the potential to decrease the incidence of helminth and intestinal protozoa infection, although heterogeneity from one community to another rendered interpretation of the results somewhat difficult [33]. Notwithstanding, a recent cluster randomized study in Mali found no effect of CLTS on diarrhea 18 months after implementation of the intervention, but a significant beneficial effect on children's anthropometric measures, as children from the intervention group were significantly less stunted [62]. Of note, the authors used a cross-sectional design for assessing diarrheal incidence at 2 time points (baseline and end line). In this protocol, diarrhea was monitored longitudinally over a 24-month period with 2-week intervals, which should capture subtle fluctuations. Two recent cluster randomized trials from India showed no effect on diarrhea, soil-transmitted helminths, and child malnutrition and highlighted the difficulty to achieve high coverage of latrine use at a large scale to demonstrate expected health outcomes [63,64].

There is considerable interest in the scientific community and among disease control program managers to bring integrated approaches into action, although the challenges of scaling up such integrated, intersectoral, multidisease control approaches are recognized [65,66]. CLTS holds promise to decrease diarrhea, helminthiasis, and intestinal protozoa infections, yet, limitations with regard to achieving open defecation-free status and sustainability exist. Our previous work in Côte d'Ivoire has provided evidence that health education interventions can improve adherence of communities to CLTS and thus increase the success rate of such an intervention [33]. A further limitation of our study is that the distance between communities was sometimes relatively small, and contamination cannot be completely excluded. Although, it has to be emphasized that in this particular study area, the difficult physical accessibility to communities can limit contamination even if communities are relatively close. Furthermore, although during the CLTS and CHEP interventions, it was emphasized that a hand washing facility needs to be provided next to the latrines (eg, bucket with water and soap) and before eating, hands need to be washed with soap, no specific water access intervention was included in the study, which might have an impact on infection outcomes.

Finally, sample size was limited by the size of the communities because of the methodological approach of CLTS. Indeed, communities up to a maximum size of 500 to 600 members are more likely to adhere to CLTS compared with larger communities.

This study and experiences gained elsewhere [67] will shed new light on the effect of integrated approaches on different

outcomes, including parasitic infections (soil-transmitted helminths, schistosomes, and intestinal protozoa), incidence of diarrhea, anthropometric measures, and KAPB of populations. Furthermore, this line of scientific inquiry will enhance our knowledge of community acceptance regarding integrated control approaches, including strengths and limitations, and provide important information for existing sanitation and health programs in Côte d'Ivoire and elsewhere.

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Authors' Contributions

GR wrote the manuscript. GR and JU revised the manuscript. EH produced the map. GR, BB, EKN, and JU designed the study. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

- CHEP:** community health education program
CLTS: community-led total sanitation
EPG: eggs per 1 g
FGDs: focus group discussions
KAPB: knowledge, attitudes, practices, and beliefs
SAF: sodium acetate-acetic acid-formalin
WHO: World Health Organization

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Protocol

Using mHealth to Increase Treatment Utilization Among Recently Incarcerated Homeless Adults (Link2Care): Protocol for a Randomized Controlled Trial

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Abstract

Background: There is a significant revolving door of incarceration among homeless adults. Homeless adults who receive professional coordination of individualized care (ie, case management) during the period following their release from jail experience fewer mental health and substance use problems, are more likely to obtain stable housing, and are less likely to be reincarcerated. This is because case managers work to meet the various needs of their clients by helping them to overcome barriers to needed services (eg, food, clothing, housing, job training, substance abuse and mental health treatment, medical care, medication, social support, proof of identification, and legal aid). Many barriers (eg, limited transportation, inability to schedule appointments, and limited knowledge of available services) prevent homeless adults who were recently released from incarceration from obtaining available case management, crisis management, substance abuse, and mental health services.

Objective: The aim of the Link2Care study is to assess the effectiveness of a smartphone app for increasing case management and treatment service utilization, and in turn reduce homelessness and rearrest. The goals of this research are to (1) assess the impact of an innovative smartphone app that will prompt and directly link recently incarcerated homeless adults to community-based case management services and resources and (2) utilize in-person and smartphone-based assessments to identify key variables (eg, alcohol or drug use, social support, psychological distress, and quality of life) that predict continued homelessness and rearrest.

Methods: Homeless adults (N=432) who enroll in a shelter-based Homeless Recovery Program after release from the Dallas County Jail will be randomly assigned to one of the three treatment groups: (1) usual case management, (2) usual case management plus smartphone, and (3) usual case management with a study-provided smartphone that is preloaded with an innovative case management app (smartphone-based case management). Those assigned to smartphone-based case management will receive smartphones that prompt (twice weekly) connections to shelter-based case managers. The app will also offer direct links to case managers (available during normal business hours) and crisis interventionists (available 24 hours a day, 7 days a week) with the touch of a button.

Results: Recruitment began in the spring of 2018, and data collection will conclude in 2021.

Conclusions: This research represents an important step toward integrated service connection and health care service provision for one of the most underserved, high need, and understudied populations in the United States.

Trial Registration: ClinicalTrials.gov NCT03399500; <https://clinicaltrials.gov/ct2/show/NCT03399500> (Archived by WebCite at <http://www.webcitation.org/6zSJwdgUS>)

Registered Report Identifier: RR1-10.2196/9868

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KEYWORDS

case management; criminal justice; treatment

Introduction

Background

An estimated 3.5 million people experience homelessness each year in the United States [1], and 6.2% of US adults have been homeless at some point in their lifetime [2]. Homeless adults are more likely than domiciled adults to be male, single, African American [3-7], have very low income, and have average life expectancies that are 8 (women) to 13 (men) years shorter [8]. Homeless adults are more likely than domiciled adults to spend time in jail [9], and as many as 32% of jailed adults report being homeless in the year before their arrest [3,9]. Furthermore, homeless adults are more likely to return to jail after incarceration than domiciled adults [10]. In Texas, more than half of adults released from county jails are rearrested within 1 year [11], and many of those rearrested are homeless [12]. In Dallas County alone, 5530 homeless adults were incarcerated in 2013 at an estimated cost of US\$12,557,406 (calculated in 2014) [13].

Incarcerated homeless adults have a variety of risk factors that increase the likelihood of rearrest. For instance, homeless inmates are more likely than domiciled inmates to have histories of mental illness or substance use disorders [9,12]. The research team's preliminary studies indicated that homeless adults released from jail in the past year were more likely than those not recently incarcerated to have a history of substance use or mental health problems [14]. Thus, there is a strong need for mental health and substance abuse treatment among homeless adults following their release from jail. Studies have indicated that case management services for substance use and psychological distress can attenuate the link between homelessness and incarceration [15-18]. The overall significance and scope of this issue was eloquently stated by Kushel and colleagues in their evaluation of the *revolving door* of homeless incarceration [16]: "High rates of imprisonment among homeless populations may be the end result of a system that does not provide access to timely services, including access to housing, health care, mental health care, and substance abuse treatment, and systems that have obstacles preventing receipt of these services by people exiting prison." Thus, individuals who leave jail and return to the community without stable housing are at increased risk for premature mortality [19,20] and rearrest [10,12] and are critically in need of interventions that increase access to services [15].

Case Management

Case management is the professional coordination of individualized care [21]. Specifically, case managers link individuals with relevant services and help them to overcome barriers to service utilization. In addition, case managers engage in client assessment, practical support, service planning, advocacy, and monitoring of service utilization and progress [17,22,23]. More intensive case management services (often employed with homeless adults) include a multidimensional approach with integrated counseling, independent living skills building, assertive outreach, and crisis intervention [24]. Case management has been shown to be effective in improving housing stability, mental health, quality of life (QoL), and social functioning, while reducing substance use, hospitalization stays, and incarceration in at-risk populations [15,25-27], including homeless and recently incarcerated adult populations (see meta-analysis [23]).

Homeless individuals have many needs following release from incarceration, including housing, employment, substance abuse and mental health treatment, medical care, medication, social support, proof of identification, and legal aid [3,9,28,29]. Although many existing public services address these needs, there are many barriers to service utilization and obtaining stable housing [30]. For example, it is difficult for an individual to identify which services and housing placement programs are and are not available to those with histories of arrest, substance abuse, and serious mental illness [15,31-33]. Furthermore, inability to provide valid identification (eg, driver's license or birth certificate) limits the ability to obtain employment assistance and disability services and is often a rationale for arrest by police [30]. In addition, lack of access to transportation reduces the ability of this population to access free and available community services (eg, food, clothing, temporary housing, and obtaining identification) [34]. There are also many specific barriers to the utilization of case management among homeless adults, including lack of a permanent address, telephone service, transportation to case management visits, and access to service providers' contact information [8,35-39]. These factors reduce the ability of homeless adults to schedule appointments and limit the ability of providers to contact patients regarding appointments [40,41].

Smartphone Use Among Homeless Adults

Cell phone ownership is common among homeless adults, with 58.4% reporting that they had active cell phone service in 2014 [42], which is not surprising because there are government programs that pay for cell phone service for qualifying very low

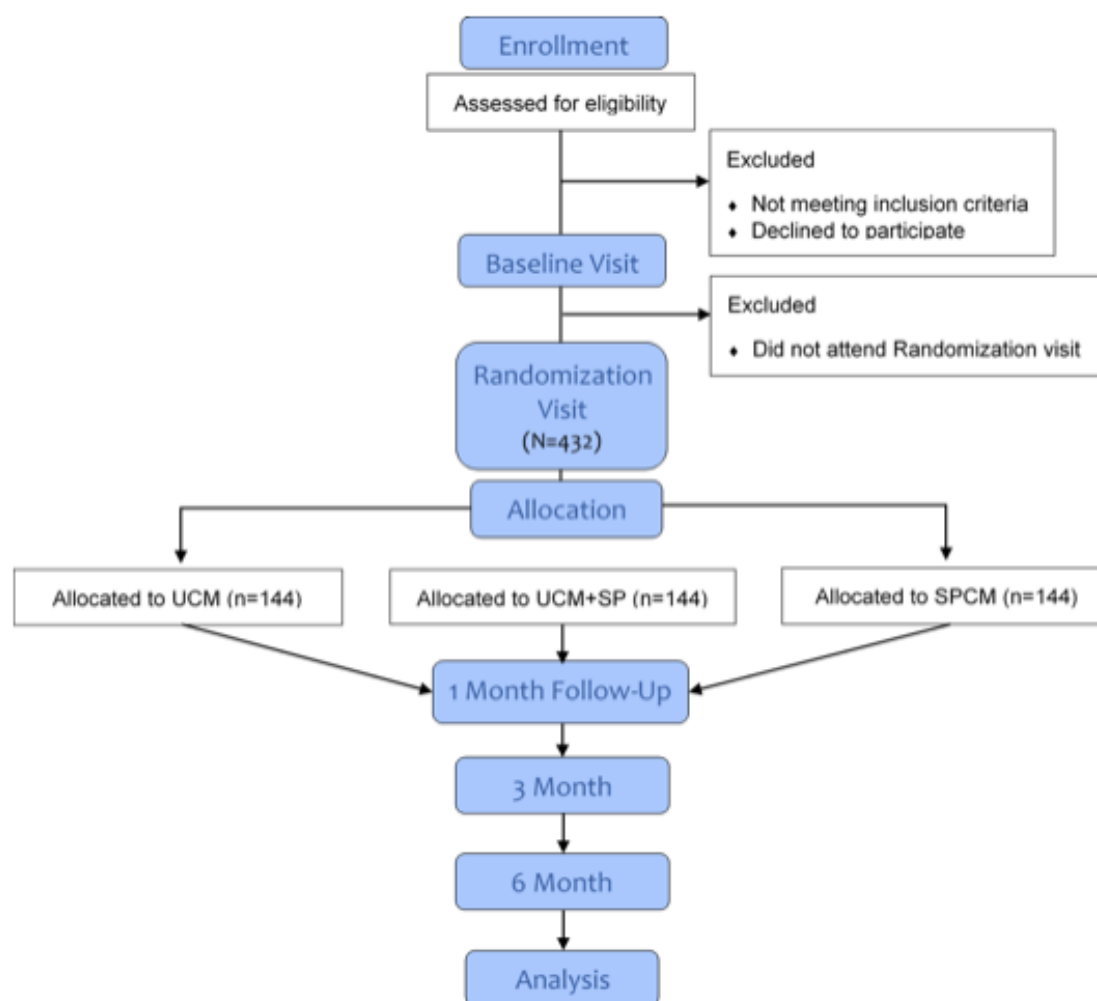
income adults [43]. Furthermore, findings from other research suggest that 71.9% of homeless adults in Oklahoma City had an active cell phone or smartphone in 2016 (56.1% had an active smartphone, unpublished data [44]). Other studies have indicated that 70% of homeless adults who have cell phones use them to connect with peers and family members, 32% carry a phone for safety reasons (eg, access to emergency services), and 23% use a phone to communicate with current or potential employers [39-41]. Although 62% of homeless youths possessed activated cell phones, only 17% were using their cell phone to connect to case managers [40]. Thus, initial evidence indicates that cell phones are already being widely used in homeless populations, but few homeless adults are using their phones to contact case managers who have the primary role of linking individuals to care and coordinating care for those in need. Thus, a significant opportunity for novel interventions is being missed. Smartphone apps may be a novel way to facilitate direct access to case management and may be a practical and affordable means by which to reduce barriers to service utilization in vulnerable and hard-to-reach populations. In our recent studies that have used smartphones, the cost for an activated smartphone with monthly talk, text, and internet has been under US \$20 per month, which is equivalent to less than the cost of one-third of 1 day in the Dallas County Jail [45].

Aside from demographic variables and history of mental illness or substance use or abuse, very few predictors of rearrest and sustained homelessness have been identified [9]. To date, all studies that have examined predictors of incarceration, rearrest, health, and continued homelessness among homeless adults have used traditional in-person assessment methods that are usually conducted retrospectively or months or years before the predicted outcome [9,16,37,46-49]. Studies have indicated that traditional assessment methodologies provide biased and inaccurate estimates because of recall bias and errors in memory (eg, assessing the number of drinks consumed or level of depression or anxiety over the past week or month) [50,51]. Ecological momentary assessment (EMA), in which handheld

devices are used to capture “real time” experiences that vary daily (or from moment to moment), is currently the most accurate way to measure phenomena in real time in natural settings [50,52]. Although EMA has been used in a variety of populations and with multiple health outcomes, only 1 study [53] outside of our own work [54] has collected EMA data in homeless adults. The current study (Link2Care) will identify key variables, measured proximally (EMA data) and distally (traditional in-person assessments and EMAs), that predict alcohol and drug use, social support, psychological distress, and QoL. These rich data will address knowledge gaps that have limited our understanding of and ability to intervene in this marginalized population.

In the Link2Care three-arm randomized controlled trial (RCT), homeless adults who enroll in a shelter-based Homeless Recovery Program following release from the Dallas County Jail (N=432) will be randomized to one of three conditions: usual case management (UCM), UCM plus smartphone, or UCM plus smartphone-based case management (SPCM). SPCM will be delivered through the Insight mHealth platform. Insight is a versatile mobile app platform that enables researchers to rapidly create and schedule smartphone-based assessments and interventions [55]. The app will not provide case management and crisis intervention services directly; rather, it will prompt twice weekly contact with their case manager and provide links to service providers through the touch of a button. Specifically, we will compare case management and crisis management service utilization among recently incarcerated homeless adults who are randomized to the UCM, UCM plus smartphone, and SPCM conditions. We will also estimate the effect of treatment condition on alcohol use, drug use, and psychological distress, and identify key factors (alcohol and drug use, social support, psychological distress, QoL) that predict rearrest and nights spent homeless using traditional and smartphone-based assessment approaches. A flowchart of the procedures is provided in [Figure 1](#).

Figure 1. CONSORT flow diagram for Link2Care randomized controlled trial. UCM: usual case management; SP: smartphone; SPCM: smartphone-based case management.



Methods

Setting and Procedure

Link2Care is an unblinded RCT. Participants (N=432) will be recruited at a large homeless shelter in Dallas, Texas. The shelter has 80 employees and on-site partners that provide services (eg, meals, mental health and substance abuse counseling, case management, housing placement, and job readiness training) to approximately 85% of all homeless adults in Dallas County each year. The shelter conducts approximately 366 new intakes each month, and approximately half of all new intakes enroll in the optional Homeless Recovery Program. Overall, the shelter provides services to 2847 unique homeless adults each month.

Eligibility Criteria

Textbox 1 shows the eligibility criteria for interested individuals.

Participant Recruitment

Individuals who identify as homeless upon release from the Dallas County Jail will be given a two-sided flier by jail reentry staff. One side of the flier will provide information about services that may be useful to homeless adults in Dallas (eg, directions to the shelter and other nearby shelters where they

may obtain meals, shelter, housing assistance, and other services). The other side of this flier will be used to briefly describe this study. Each flyer will have a unique identification number to allow the researchers to track the response rate based upon the number of flyers distributed. This flyer will be considered a “ticket” for screening and potential participation into this study.

Individuals who were released from the Dallas County Jail in the past month and present at the shelter will complete a shelter intake form and enroll in the shelter’s Homeless Recovery Program (this is the current standard of care at the shelter). These individuals will receive information about this study and will be informed that shelter services are not contingent upon study enrollment. Eligible adults who remain interested the study will be directed by the shelter intake coordinator to the study research staff for screening.

Those who meet study inclusion criteria and provide informed consent will complete the baseline assessment measures and will be given an appointment to return to the shelter within 72 hours for randomization into one of three study conditions. Participants will return to the shelter for follow-up assessments 1, 3, and 6 months after the randomization visit. All participants,

regardless of condition, will be compensated for completing each in-person visit.

During the informed consent process, a member of the research team will explain to all participants that no information that they provide during the study will be shared with the Dallas County Jail. The research team will also discuss our Certificate of Confidentiality with each prospective participant and how the Certificate will be used to refuse requests to disclose information from all outside organizations, including Dallas County.

Randomization Plan

We will use permuted-block randomization to avoid the disadvantage of simple randomization where treatment imbalance can occur periodically. We will use a block size of 12 to ensure that an equal number of 4 subjects are randomized into each arm within an individual block. On the basis of our total sample size of 432, we will perform permuted-block randomization for a total of 36 blocks.

Study Conditions

Usual Case Management Group

The UCM group will receive the standard Homeless Recovery Program currently offered at the shelter. To qualify for the standard Homeless Recovery Program, individuals must complete a shelter intake and substantiate homelessness (eg, provide evidence that they spent the previous night in a shelter or jail). The shelter intake includes a comprehensive needs assessment, and demographic information is obtained. Following intake, shelter guests receive a day pass that grants them access to many of the services available at the shelter (eg, meals, showers, laundry, phone, mail, library, barber shop, and storage space for their belongings). Those who enroll in the shelter's Homeless Recovery Program receive an identification card and can gain access to additional services including case management, onsite mental health and substance abuse counseling, housing assistance, disability or veterans benefits assistance, job readiness training, legal aid, and bus passes.

Although these services are freely available to all guests enrolled in the Homeless Recovery Program, many services are offered only during normal business hours, and in-person visits are the norm.

Shelter case managers are licensed professional counselors or Master's level clinicians who adhere to the Standard Case Management Model [23,58]. Case managers assist homeless adults with (1) Developing care and housing plans, (2) Making and maintaining linkages to on- and off-site service providers (eg, mental health and substance abuse treatment providers), (3) Obtaining vital documents needed for housing and income (eg, birth certificates, state identification, and social security cards), (4) Job readiness training and placement (if appropriate), (5) Overcoming barriers related to criminal history, (6) Development of and reconnection with support systems, and (7) Transitioning from homelessness to appropriate housing. Case managers also advocate on behalf of homeless adults by serving as a connection between all agencies that will be assisting the guest, their families, and any other involved parties. Guests are encouraged to meet with their case managers weekly; however, shelter data have indicated that those who enroll in the shelter's Homeless Recovery Program complete a total of 1.95 and 3.12 case management sessions, on average, in the first 1 and 6 months of enrollment, respectively.

Shelter intake specialists are primarily responsible for completing the shelter intake process with shelter guests, determining eligibility for the shelter's Homeless Recovery Program and ensuring that guests are linked with onsite case management staff and the on or off-site service providers they need (eg, mental health and substance abuse programs). The intake process includes collection of information on behavioral and mental health and treatment history, substance abuse and treatment history, risk and safety assessment, medical history, criminal history, history of homelessness, and assessment of social support and other protective factors. Intake specialists are available to meet with guests at the shelter and over the phone.

Textbox 1. Eligibility criteria.

Interested participants are eligible for the study if they

- were released from Dallas County Jail in the past month
- plan to reside in the Dallas area for the next year
- enroll in the shelter's Homeless Recovery Program
- are willing and able to attend the baseline visit, randomization visit, and the 1-, 3-, and 6-month follow-up visits
- score ≥ 4 on the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) [56], indicating >6 th grade English literacy level (ie, a 7th grade reading level is necessary to complete assessments; $<1\%$ of shelter guests are non-English speakers)
- score >24 on the Mini-Mental State Exam [57], indicating no substantial cognitive impairment

Table 1. Smartphone-based case management (SPCM) group smartphone app features.

Feature or button	Description of feature
Call My Care Manager	Clicking this button will automatically call the participant's assigned case manager. Individual case managers are assigned to all Homeless Recovery Program enrollees, and they are available from 8:00 AM to 5:00 PM Monday to Friday.
Call Crisis Line	Clicking this button will call a representative from a Dallas-based crisis line available 24 hours a day, 7 days a week to help homeless individuals address and overcome crises.
Helpful Websites	Clicking this option will lead to a menu of websites that may be useful to participants (eg, Dallas public transit routes and support group schedules or locations [eg, Narcotics and Alcoholics Anonymous]).
Call Study Staff	Clicking this option will connect participants to study staff if they encounter problems with the study phone or rescheduling missed follow-up appointments.
Payment	This button indicates the amount of incentives that participants have earned for completing ecological momentary assessments to date. These payments will be awarded when each participant presents at the shelter to complete their 1-, 3- and 6-month follow-up assessments.

Usual Case Management + Smartphone Group

The UCM plus smartphone group will receive UCM and an activated study smartphone (described below), even if they own a personal cell phone. This smartphone only group (without the SPCM app) is necessary to differentiate the effect of the innovative app from provision of a smartphone only. Homeless adults who have phones and access to the internet may have higher levels of social support, which may be related to mental health, QoL, and ability to obtain housing and avoid rearrest [8,41,59]. All smartphones will include standard cellular service that includes unlimited SMS text messaging (short message service), talk minutes, and internet access (speeds are throttled after monthly download limit is reached). Participants will be informed that they may use the phone to make calls, text, and use the internet as they wish during the 6-month course of the study. Participants randomized to the UCM plus smartphone condition will receive phones with a very basic app that will include only the "Call Study Staff" and "Payment" functions (see Table 1 and Figure 2) on the app home screen and will prompt daily EMAs (see EMA description below). Links to case management resources will not be loaded onto phones for participants in UCM plus smartphone condition.

Smartphone-Based Case Management Group

Participants who are assigned to SPCM will have access to UCM and will receive a smartphone that is preloaded with an app that will provide direct links to services. Participants will be asked not to discuss SPCM app features with other participants. Smartphones and service plans will be identical to what is provided to the UCM plus smartphone group. SPCM and UCM plus smartphone condition participants will keep the phones at the end of the study.

Recent research has indicated that phone prompts can increase service utilization [60,61]. For example, Lucht showed that twice weekly phone prompts increased phone-based counseling sessions in alcohol dependent patients [60]. To increase the likelihood that SPCM group participants will use the resources available through the app, the phone will be programmed to automatically prompt or suggest a connection with their case manager twice per week. Specifically, the phone will ring or

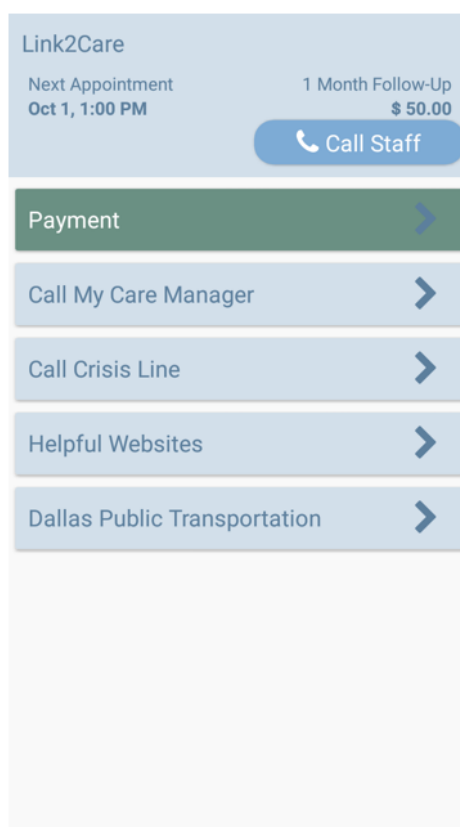
vibrate on two occasions each week at random times between 9:00 AM and 5:00 PM, Monday to Friday, to ask participants if they would like to contact their case manager. Participants will be able to select "No" (this will decline the connection) or "Yes" (this will automatically call their case manager). Participants will be instructed to leave a voice message or speak with an alternate case manager when their case manager cannot be reached. We decided against more frequent prompts to connect with case managers (eg, daily) because of higher participant burden and concern for overwhelming the case management system.

Participants who are randomly assigned to the UCM plus smartphone or SPCM conditions will receive a smartphone at the randomization visit, and they will be asked to carry it with them at all times for 6 months (26 weeks). Date, time, and duration of SPCM app feature use (eg, case manager calls) will be recorded by the app for future analysis. See Table 2 for a summary of study conditions.

Measures

Traditional Measures (In-Person)

Traditional assessment data will be primarily collected on laptop or tablet computers using Questionnaire Development System (QDS) software at in-person baseline and follow-up visits. QDS utilizes a computer-administered self-interview format (ie, *audio computer-assisted self-interviewing*) that reduces data entry errors and the need to retain paper copies of raw data. Each item appears on the computer screen while the program simultaneously reads the item (participants may select their responses only after QDS reads each item). Participants wear headphones so that others do not hear the survey items. Participants have reported few problems using the QDS program, including those with no computer experience. Staff will be available to help participants who may have difficulty. The amount of time needed to complete the QDS-administered questionnaires varies by study visit. On the basis of our previous experience with collecting data in homeless adults, we estimate that the baseline visit will require approximately 1.5 hours to complete, and follow-up assessment visits will require approximately 1 hour.

Figure 2. Smartphone-based case management app.**Table 2.** Summary of study conditions.

Participants receive	UCM ^a	UCM + plus smartphone	SPCM ^b
Standard intake with service referrals	✓	✓	✓
Standard Homeless Recovery Program	✓	✓	✓
Shelter care managers and crisis management	✓	✓	✓
Provided study smartphone		✓	✓
Provided study smartphone with care linkage app and prompts			✓

^aUCM: usual case management.

^bSPCM: smartphone-based case management.

Traditional measures are listed in [Textbox 2](#). [Textbox 3](#) includes numerous constructs that are hypothesized to directly and indirectly (ie, mediation of the treatment effect) affect the study outcomes. In addition, barriers to phone-based case management sessions and staff and participant perceptions of the SPCM app will be assessed. Finally, participants will be asked if they handled or were aware of other participants' study phones to assess potential cross contamination between study arms. Rearrest and number of homeless nights will be collected using a Timeline Follow-back procedure at all in-person study visits. In addition, arrest data from the Dallas County Jail will be examined to identify participants who are rearrested within 12 months of the randomization visit. This will provide an objective measure of the date and time of arrest, as well as a description of the charges.

Ecological Momentary Assessment Measures (Phone-Based)

EMA is currently the most accurate way to measure phenomena in near real time in natural settings [50,52]. Thus, EMA methodology will enable the identification of key variables that predict study outcomes with less bias than traditional in-person assessments. At the randomization visit, those assigned to the UCM plus smartphone and SPCM conditions will be trained on how to use the smartphone to complete EMAs and how to use the "Call Staff" and "Payment" button or options. Those assigned to the SPCM condition will be trained to use the features of the full smartphone app. All participants who receive smartphones will be prompted by the phone to complete one EMA 30 min after waking each day for 6 months beginning on the day of the randomization visit. EMA data, collected over a 6-month period, will be used to identify factors that significantly

contribute to alcohol or drug use, QoL, social support, distress, rearrest (ie, because rearrest rates tend to peak within 6-12 months of jail discharge [11]), and continued homelessness (homeless episode duration peaks at 180-190 days [76,77]).

Hardware

Participants will use Samsung Galaxy Core Prime smartphones (or equivalent) to complete EMAs. The phone has a 4.5 inch (480x800 pixel resolution) touch screen display, a built-in microphone, earphone jack, speaker, and a rechargeable battery with 13 hours of talk time. It is Wi-Fi and Global Positioning System capable. Participants will navigate through the EMA program and enter data simply by touching the screen. Thus, computer or typing skills are not required. Participants have the ability to call (eg, if they have problems completing EMAs) and receive calls from research staff through the smartphone free of charge.

Programming

The mHealth Shared Resource at the University of Oklahoma Health Sciences Center and Stephenson Cancer Center will provide the programming services for the proposed project [55]. The mHealth Shared Resource specifically offers resources that

empower researchers to build, test, and launch technology-based assessment and intervention tools. Apps are developed using state-of-the-art cross-platform (eg, Android and Apple) design tools. The mHealth resource employs a program manager and four mobile app programmers who develop and maintain Web and mobile apps and relational databases.

Ecological Momentary Assessments

The EMA methodology that will be used in this study is similar to that developed by Shiffman and colleagues [51,78,79] and was used in previous studies conducted by the investigative team [80-84]. EMA items will assess numerous constructs that are hypothesized to be related to the study outcomes (see [Textbox 3](#)). The phone will audibly and visually cue EMAs for 5 min and 30 min after each participant's preset waking time. If the participant does not respond to the initial EMA prompt, the EMA will be recorded as missed, and another prompt will be pushed 1 hour later (this will reduce the likelihood of missed EMAs). On average, EMAs are expected to take 3 to 4 min to complete. All EMAs will be date-, time-, and geolocation-stamped for future analyses. A Certificate of Confidentiality has been obtained from the National Institutes of Health to protect participant data from subpoena.

Textbox 2. Example in-person measures.

In-person measures

1. Demographics or background
 - Demographics and Homelessness Questionnaire
 - Arrest history [62]
2. Health, mental health, and health behavior
 - Patient Health Questionnaire (depression or anxiety) [63]
 - Mental Health Component from the 12-item Short Form Survey (SF-12) [64]
 - Health-related quality of life [65]
 - Alcohol and drug timeline follow back [66]
3. Stress or stress measures
 - Discrimination [67]
 - Urban Life Stressors Scale [68]
 - Personal victimization [69]
 - Perceived Stress Scale- Short Version [70]
4. Negative affect
 - Aggression [71]
 - Center for Epidemiological Studies-Depression (CES-D) [72]
5. Interpersonal or intrapersonal resources
 - Interpersonal Support Evaluation List-12 [73]
 - Lubben Social Network Scale-6 [74]
6. Homeless Nights Timeline Follow Back [75]
7. Treatment Quality and Satisfaction Survey

Textbox 3. Ecological momentary assessment (EMA) items.

1. Daily items
 - Positive and negative affect
 - Sleeping arrangements
 - Social support and interactions
 - Stressors
 - Discrimination
 - Prescription medication use
 - Alcohol consumption
 - Other illicit substance use
 - Meal consumption
2. Weekly: Monday assessments
 - Arrest
 - Employment
 - Exposure to crime or violence
 - Emergency room visits
 - Hospitalization
 - Quality of life

Smartphone Training

We have developed and successfully implemented a brief user-friendly training protocol for those with limited or no experience using smartphones. Participants will receive hands-on training on study phone use and will watch a brief step-by-step video tutorial (created by the researchers) that demonstrates use of the study smartphone and app features. This video is preloaded onto the home screen of each study phone so that participants may watch and rewatch it at any time. The investigators have achieved high EMA compliance rates (ie, 90.6%, 802/885) of morning EMAs completed) using this protocol in a sample of homeless adults [85].

Compensation

Participants will receive compensation for completing each in-person visit (ie, visits 1 and 2=US \$30; visits 3-5=US \$50) in the form of gift cards. Participants who receive study phones will also be compensated based upon the percentage of EMAs completed since their last in person visit. At the 1-month follow-up visit, participants who completed >90% of daily EMAs will receive a US \$50 gift card, those who completed 75% to 89% of EMAs will receive a US \$30 gift card, and those who completed 50% to 74% of EMAs will receive a US \$20 gift card. Thus, participants may receive up to US \$50 for completing EMAs at the 1-month follow-up visit, US \$100 at the 3-month follow-up visit (2 months of EMA), and US \$150 at the 6-month follow-up visit (3 months of EMA).

Data Loss Prevention

To overcome potential loss of data if participants lose the study phone, phones will be programmed to connect to the secure server each day to upload encrypted data. This will ensure that

no collected EMA data are lost. This tactic will also allow the researchers to remotely monitor each participant's EMA completion rate and intervene (eg, call the participant) when this rate is low. Importantly, EMA data will be password-protected and encrypted on the study phone, and only encrypted data are transmitted to the secure server. Thus, study data are only accessible by the research team. If a phone is lost or damaged, it will be remotely cleared of data, and only one replacement phone will be provided to each participant.

Participant Emergencies

Participants in all three conditions will be informed that they should utilize the Bridge Homeless Recovery Program or call 911 to manage mental health issues and crises. In addition, participants who are assigned to the SPCM group will be informed that they can click the "Call Crisis Line" button to obtain further assistance in crisis situations. If the participant expresses suicidal plans, symptoms of major depression, panic attacks, acute withdrawal symptoms, etc, during interactions with research staff at scheduled study visits at the Bridge shelter, staff will facilitate immediate connection with Bridge case managers.

Sample Size

The number of participants (n=144 in each group) was estimated based on the following assumptions: (1) random allocation of participants between three conditions, (2) type I error rate set to 0.05, (3) a 30% dropout rate for each condition [27], (4) targeted minimum power of 0.9, and (5) a conservative increase of 4.5 case management sessions between the UCM and SPCM conditions across the 6-month study period. The estimated increase in case management sessions is based on a previous study [60] showing that 20% of all phone-based prompts to

connect with an alcohol treatment counselor resulted in actual treatment sessions.

Statistical Analysis

Primary analyses will model counts of the total number of case and crisis management sessions that occurred between the randomization visit and the 6-month follow-up across the three conditions using linear regression, with indicator variables to compare the effect of each study group, adjusting for controlled covariates (race or sex or age). We will also perform stratified modeling to determine if the intervention has similar effects across races, sexes, and age. We will adjust for multiple comparisons using the false discovery rate adjustment [86]. For all statistical analyses, the necessary assumptions will be tested before modeling. Remedial measures include variable transformation or generalized linear modeling (such as Poisson regression).

Multilevel models, also known as mixed models, will assess the effect of condition on alcohol and drug use and psychological distress. Covariates for analyses will include baseline characteristics that are known predictors of each outcome, including age, race or ethnicity, employment status, criminal history, and periods of lifetime homelessness. We will also test for interactions between treatment and key demographic variables (eg, race, ethnicity, sex, and age).

Logistic regression of traditional in-person assessments (eg, substance use, social support, psychological functioning, and QoL; see [Textbox 3](#) for other key constructs) and summarized EMA data (eg, affect, stress, discrimination, and alcohol and drug use; see [Textbox 3](#)) will be conducted to identify significant demographic, psychosocial, environmental, and behavioral predictors of rearrest in the 12 months following the randomization visit (rearrest status is a binary outcome). Covariates may include treatment group, age, sex, race or ethnicity, education, type of crime, and other variables as appropriate. Change scores (eg, change in social support from baseline to the 1-month follow-up visit) will also be examined as potential predictors of rearrest. If little variation in rearrest status is detected, supplementary survival analyses may be conducted to identify predictors of time to rearrest.

Generalized linear mixed model (GLMM) regression analyses will be used to examine the longitudinal effect of key risk and protective factors on number of homeless nights (measured repeatedly using a timeline follow-back procedure at in-person follow-up visits). GLMM can handle fixed and random effect model parameters, nested designs, and repeated measures with various correlation structures [87,88]. GLMM can also handle different variance functions, unbalanced designs where the number of repeated observations varies across individuals, and the situation where assessments within a week are more highly correlated than assessments separated by multiple weeks or months. We will assess the best way to model the correlation of the repeated measures using the methods of Wolfinger [89] and statistics such as Akaike's and Schwarz's information criteria. Adjustments for multiple comparisons will be made according to Westfall and Young [90].

GLMM will also be used to identify proximal predictors of homeless nights (assessed each day) using EMA data. EMAs generate an enormous amount of data; therefore, we will be able to address multiple within- and between-subject questions. For example, key EMA variables (eg, negative affect and stress) and parameters (eg, intercept, slope, quadratic term, and volatility) will be examined as potential predictors of homeless nights. This invaluable information may be used to detect high-risk situations that may be targeted in future "just-in-time adaptive interventions." EMA data will also allow us to address other important exploratory questions such as (1) What psychosocial changes occur as an individual moves from homelessness into housing and (2) What effect do events such as exposure to discrimination, violence, or hospitalization have on homeless nights and reincarceration.

Finally, the PROCESS macro for SPSS or SAS (described in Hayes [91] and available online [92]) will be used to conduct exploratory mediation analyses to identify variables that mediate the relation between condition and homeless nights and rearrest outcomes. This method uses an ordinary least squares path analytic framework to estimate direct and indirect effects in single and multiple mediation models with bootstrapped CIs. The macro can also be used to evaluate moderated mediation models, including those with dichotomous outcomes (eg, arrest vs no arrest).

Results

Two separate institutional review boards (IRBs), the Committee for the Protection of Human Subjects at the University of Texas School of Public Health (IRB approval HSC-SPH-15-0632) and the University of Oklahoma Health Sciences Center (IRB approval 8525), have approved the protocol as presented in this manuscript. The smartphone app has been developed (see [Figure 2](#) for a screenshot of the SPCM app home screen), and data collection began in April 2018. Participants will be enrolled for 6 months, and rearrest data will be collected over a 12-month period.

Discussion

Research Goals and Hypotheses

Link2Care will be the first study to use smartphones to increase case management sessions among homeless adults. If effective, smartphone apps that remove or attenuate barriers to case and crisis management services could be easily incorporated into other "real world" settings to reduce health disparities among homeless adults. Specifically, we hypothesize that recently incarcerated homeless adults assigned to the SPCM condition will utilize more case and crisis management services than those assigned to UCM or UCM plus smartphone condition. Our study will also compare the effect of treatment condition on alcohol use, drug use, and psychological distress, and we expect that the SPCM group will demonstrate greater improvements in each outcome compared with UCM plus smartphone or UCM. Finally, we will identify key factors (alcohol and drug use, social support, psychological distress, QoL) that predict rearrest and nights spent homeless using traditional and smartphone-based assessment approaches. We hypothesize that key variables that

are measured in-person (eg, alcohol or drug use, perceived social support, psychological distress, and QoL) and via daily phone-based assessments (eg, affect, stress, discrimination, and alcohol or drug use) will have direct effects on rearrest and number of homeless nights. These key variables are also hypothesized to mediate the relation between treatment condition and number of homeless nights and rearrest.

We expect that Link2Care will have an important and sustained impact by (1) providing evidence of the utility and effectiveness of an innovative, low cost, highly disseminable, and sustainable smartphone app that links a vulnerable population to freely available services and (2) identifying key mechanisms of treatment that may become intervention targets in future research. It is also conceivable that the SPCM app may reduce victimization, as the overlap between victimization and offending is well-documented [93], especially among those with mental health problems [94]. If effective, efforts will be made to disseminate the app to criminal justice agencies and shelters nationwide.

Potential Problems and Alternate Strategies

We expect follow-up rates that align with those attained in our previous studies (eg, in one of our previous studies with a similar homeless population, 96% of all participants attended the 1-week and 2-week follow-up visits [when they were carrying the smartphone], and 79% attended the 5-week follow-up visit) [86]. In Link2Care, two-thirds of all participants will be reachable through study phones, and we anticipate high follow-up rates for these participants. We have made efforts to ensure high follow-up rates for those assigned to UCM (they

do not receive study phones). Specifically, participants will be asked to provide detailed contact information [95]. These forms have been used to maintain contact with 78% to 88% of recently incarcerated or homeless adults for up to 12 months after enrollment [64,96-98]. In addition, a shelter case manager will assist with contacting participants whom research staff are unable to contact directly using the participant contact form [95,97]. It is important to note that many homeless adults have mailboxes at the shelter, and their forwarding address is obtained when they obtain housing. If participants do not have transportation, bus passes will be mailed to the participants' desired location so that they can attend follow-up visits (many local shelters offer onsite mailboxes). Should high rates of missing data occur, we will employ multiple imputation methods designed for longitudinal data [64], such as R packages *mice* [99] and *pan* [100]. Other studies comparing usual care with a smartphone intervention have observed equal rates of attrition across study arms [101,102].

Impact

Future research will refine the app for testing and dissemination to other homeless populations. Results from the Link2Care study will provide information that may be used to develop novel phone-based interventions that use EMAs to detect risky thoughts, behaviors, and situations in real time and automatically intervene (eg, calling counselors and text-based suggestions for dealing with mood or coping with stress). Future research studies will be conducted to determine the cost effectiveness of smartphone-based case management interventions, which may be lower than the cost of traditional case management or incarcerating or hospitalizing homeless adults.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer review summary statement.

[[PDF File \(Adobe PDF File\), 305KB - respot_v7i6e151_app1.PDF](#)]

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Abbreviations

EMA: ecological momentary assessment
GLMM: generalized linear mixed model
IRB: institutional review board
QDS: Questionnaire Development System
QoL: quality of life
RCT: randomized controlled trial
SPCM: smartphone-based case management
UCM: usual case management

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Protocol

A Self-Paced, Web-Based, Positive Emotion Skills Intervention for Reducing Symptoms of Depression: Protocol for Development and Pilot Testing of MARIGOLD

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Abstract

Background: Living with elevated symptoms of depression can have debilitating consequences for an individual's psychosocial and physical functioning, quality of life, and health care utilization. A growing body of evidence demonstrates that skills for increasing positive emotion can be helpful to individuals with depression. Although Web-based interventions to reduce negative emotion in individuals with depression are available, these interventions frequently suffer from poor retention and adherence and do not capitalize on the potential benefits of increasing positive emotion.

Objective: The aim of this study was to develop and test a Web-based positive emotion skills intervention tailored for individuals living with elevated depressive symptoms, as well as to develop and test enhancement strategies for increasing retention and adherence to that intervention.

Methods: This study protocol describes the development and testing for Mobile Affect Regulation Intervention with the Goal of Lowering Depression (MARIGOLD), a Web-based positive emotion skills intervention, adapted for individuals with elevated depressive symptomatology. The intervention development is taking place in three phases. In phase 1, we are tailoring an existing positive emotion skills intervention for individuals with elevated symptoms of depression and are pilot testing the tailored version of the intervention in a randomized controlled trial with two control conditions (N=60). In phase 2, we are developing and testing three enhancements aimed at boosting retention and adherence to the Web-based intervention (N=75): facilitator contact, an online discussion board, and virtual badges. In phase 3, we are conducting a multifactorial, nine-arm pilot trial (N=600) to systematically test these enhancement strategies, individually and in combination. The primary outcome is depressive symptom severity. Secondary outcomes include positive and negative emotion, psychological well-being, and coping resources.

Results: The project was funded in August 2014, and data collection was completed in May 2018. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018.

Conclusions: Findings from this investigation will enable us to develop an optimal package of intervention content and enhancement strategies for individuals with elevated symptoms of depression. If this intervention proves to be effective, it will provide a cost-effective, anonymous, appealing, and flexible approach for reducing symptoms of depression and improving psychological adjustment through increasing positive emotion.

Trial Registration: ClinicalTrials.gov NCT01964820 (Phase 1); <https://clinicaltrials.gov/ct2/show/NCT01964820> (Archived by WebCite at <http://www.webcitation.org/6zpmKBcyX>). ClinicalTrials.gov NCT02861755 (Phase 2); <https://clinicaltrials.gov/ct2/show/NCT02861755> (Archived by WebCite at <http://www.webcitation.org/6zpmLmy8k>).

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KEYWORDS

emotions; depression; telemedicine; happiness; mobile apps

Introduction

Background

According to the Centers for Disease Control and Prevention, 7.6% of Americans reported moderate to severe symptoms of depression between 2009 and 2012 [1]. Living with elevated symptoms of depression can have debilitating consequences for an individual's psychosocial and physical functioning, quality of life, and health care utilization [2-4]. Moreover, elevated depressive symptomatology is a significant risk factor for developing major depression [5,6]; has been associated with increased cardiovascular morbidity and mortality [7], risk of disability [8]; and carries an estimated annual economic cost of US \$210.5 billion [9]. However, the majority of Americans with elevated symptoms of depression go untreated or undertreated [10]; many individuals lack access to treatment or do not utilize available services [11-13]. Researchers have begun advocating for early intervention in the prevention of depression, highlighting the importance of targeting at-risk subgroups [14,15] such as those with elevated symptoms of depression [5].

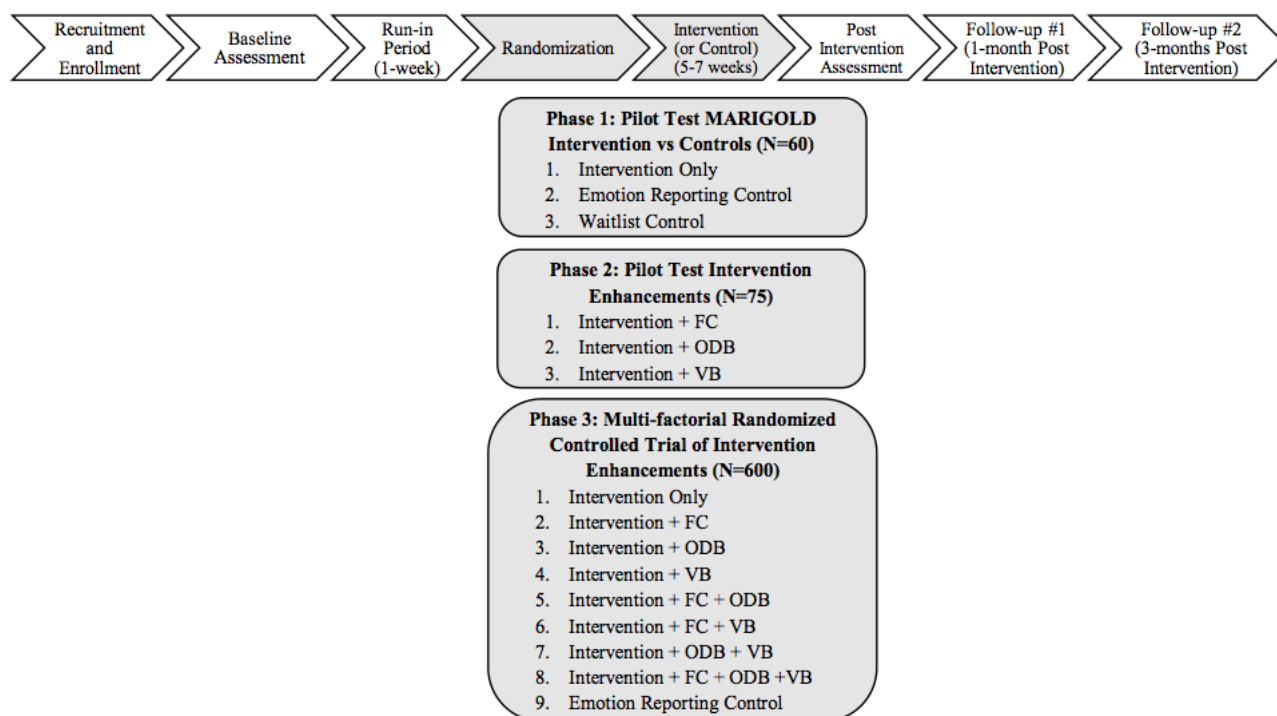
Most research has focused on the role of negative emotion in depression, while largely ignoring the role of positive emotion. However, there is considerable evidence suggesting that positive and negative emotion are not simply opposite ends of a single continuum; rather, positive and negative emotion appear to be independent of one another [16,17], can be experienced concurrently [18-20], and positive emotion appears to play a unique role in influencing physical, psychological, and social functioning, over and above the effects of negative emotion [21-23]. In fact, emerging evidence suggests that low positive emotion, in particular, plays a uniquely important role in predicting depressive symptomatology, independent of negative emotion [24-27]. For instance, low positive emotion has been found to prospectively predict the initial onset of a depressive episode [28], and the dampening of positive emotion has been linked with increased symptoms of depression [29-32]. These findings, together with a growing body of evidence highlighting the unique benefits of positive emotion for coping with negative life events more generally [33-35], suggest that increasing positive emotion is a promising pathway to target for reducing symptoms of depression.

Indeed, interventions that target increasing the frequency of positive emotion experienced in daily life appear to be helpful for reducing symptoms of depression: a meta-analysis of 25

single and multicomponent interventions focusing on increasing positive emotional states such as gratitude, happiness, and optimism found that positive emotion skills interventions showed a medium effect size for relief of depressive symptoms, with stronger effects for currently depressed participants relative to nondepressed participants [36]. These interventions show comparable efficacy and long-lasting effects as that of psychotherapy or pharmacotherapy treatments [36,37]. Furthermore, positive emotion skills interventions may help counteract the depression-related motivational deficits that can lead to poor adherence and retention in traditional psychological interventions [36,38].

The internet offers a method for delivering psychological interventions that is time- and resource-efficient and has the benefit of providing treatment to those who may otherwise lack access to available services [39,40]. Moreover, Web-based interventions have the potential to overcome many of the barriers to help-seeking that depressed individuals have reported in the past, including cost, a shortage of trained professionals, concerns about anonymity, convenience, perceived stigma, and ease of accessibility [11,13,41]. For the past two decades, a large number of internet-based interventions for depression have been developed and tested [42], and meta-analyses have indicated that such Web-based interventions can be effective at reducing depressive symptomatology [43-45]. However, many Web-based interventions tend to suffer from poorer adherence and retention [37,46,47], and these issues can be exacerbated in depressed samples, potentially because of the specific psychological features of depression, including pessimism, low motivation, loss of energy, and impaired concentration [45,47-49].

Web-based interventions that are supported by a trained professional (eg, having a trained professional associated with the study guide the participant through the intervention content via email or telephone) have been found in meta-analyses to produce larger effect sizes and better adherence relative to Web-based interventions that are self-guided [43,50]. For instance, one meta-analysis found that the average percentage of fully adherent participants (participants who completed all sessions in the intervention) was 26% for self-guided Web-based interventions versus 72% for supported interventions [50]. However, a disadvantage of supported interventions is that they tend to be more time-intensive, costly, and difficult to disseminate relative to self-guided interventions. This research aims to develop and test low-cost, resource-efficient, and scalable strategies for promoting adherence and retention in Web-based interventions.

Figure 1. Flowchart of study timeline for phases 1 to 3. FC, facilitator contact; ODB, online discussion board; VB, virtual badges.

Our team has previously developed a multicomponent positive emotion skills intervention for individuals coping with the stress of chronic illness (eg, metastatic breast cancer, HIV, and type 2 diabetes) [51-54]. In our studies, this intervention was found to have reduced depressive symptom severity when administered either in person or online, had high retention even among individuals with high levels of depressive symptoms [51-53], and was associated with increased positive emotion in the midst of stressful life events [52-54]. In this investigation, we are adapting and tailoring the intervention to maximize acceptability and relevance for individuals experiencing elevated levels of depression. In addition, this research aims to address the issues of poor adherence and retention that have plagued previous Web-based interventions.

Objectives

In this protocol paper, we describe the development and pilot testing of Mobile Affect Regulation Intervention with the Goal of Lowering Depression (MARIGOLD), a Web-based positive emotion skills intervention for individuals with elevated depressive symptomatology. We are adapting an existing multicomponent positive emotion skills intervention [51-54] and tailoring it for individuals experiencing elevated levels of depressive symptoms. In addition, we are developing and testing three enhancements aimed to boost retention and adherence to the internet-based intervention. MARIGOLD is a five-session intervention designed to teach participants eight skills for increasing positive emotion in their daily lives. The intervention development is taking place in three phases (see Figure 1).

In phase 1, we are adapting the Web-based positive emotion skills intervention to maximize the acceptability and relevance of the intervention content for people with elevated symptoms of depression and are pilot testing the tailored version of the intervention. In phase 2, we are pilot testing three enhancements

aimed at boosting retention and adherence: (1) facilitator contact, (2) an online discussion board (ODB), and (3) virtual badges. In phase 3, we are conducting a multifactorial, nine-arm pilot trial with 600 participants to systematically test each enhancement strategy, alone and in combination, for retention and adherence. The objectives of this investigation are to (1) test the feasibility and acceptability of a Web-based positive emotion skills intervention tailored for people experiencing elevated depressive symptoms (phases 1-3), (2) test the efficacy of three enhancement strategies (facilitator contact, ODB, and virtual badges) for increasing retention and adherence to the intervention (phases 2 and 3), and (3) test the preliminary efficacy of the positive emotion skills intervention for reducing depressive symptom severity (primary outcome), as well as for improving positive and negative emotion and other indicators of psychological adjustment (eg, perceived stress and meaning and purpose; secondary outcomes). Ultimately, this research seeks to develop an optimized Web-based positive emotion skills intervention, adapted for people experiencing elevated depressive symptoms.

Methods

Overview of Study Design

In each of the three phases of the MARIGOLD study, individuals with elevated symptoms of depression participate in the same flow of events (see Figure 1). The three study phases differ primarily in terms of the randomization groups and intervention portions of the study sequence (see Figure 1). Specifically, in phase 1, we are tailoring an existing positive emotion skills intervention for individuals with elevated symptoms of depression and are pilot testing the tailored version of the intervention in a randomized controlled trial (RCT) with two control conditions (N=60). In phase 2, we are developing

and testing three enhancements aimed at boosting retention and adherence to the Web-based intervention (N=75): facilitator contact, an ODB, and virtual badges. In phase 3, we are conducting a multifactorial, nine-arm pilot trial (N=600) to systematically test these enhancement strategies, individually and in combination. Each component of the study design is described in further detail below.

Participants

Study Setting

All aspects of the study (recruitment, consent, intervention, and assessments) are conducted online.

Eligibility Criteria

To be eligible for participation in any of the three pilot trials (phases 1-3), participants must meet the criteria provided in [Textbox 1](#).

Respondents are ineligible if they have already participated in a prior phase of the study. All procedures are approved by the institutional review boards at participating institutions (University of California, San Francisco, UCSF and Northwestern University), and all participants are providing informed consent. The study was registered with Clinicaltrials.gov; phase 1 at UCSF (#NCT01964820) and phase 2 at Northwestern University (#NCT02861755).

Participant Timeline

See [Figure 1](#) for the flow of events for participants in all three phases of the MARIGOLD study.

Ethics Approval and Consent to Participate

All procedures are approved by the Institutional Review Boards at participating institutions (UCSF and Northwestern University), and all participants provided informed consent. All staff members underwent updated Human Subjects Research Training either through the Collaborative Institutional Training Initiative or the NIH Human Subjects Training Module.

Recruitment and Enrollment

Participants for all three pilot trials (phases 1-3) are recruited online and online consent is obtained from each participant. We use online advertisements on platforms such as Reddit, posting within discussion threads for depression, stress, coping, and psychology. Recruitment links are also posted on Craigslist, Backpage, clinicaltrials.gov, and emailed to potential participants via ResearchMatch. Advertisements contain a link

to a Web-based eligibility screener (see inclusion and exclusion criteria above). In phases 1 and 2, eligible individuals are contacted by our research staff via telephone, and the research staff describes the study and answers any questions that participants may have. Following the telephone call, the research staff sends an email to potential participants that includes a link to the online consent form. In phase 3, our team eliminated the telephone call and replaced it with an online instructional video. Potential participants in phase 3 take the Web-based screener, and eligible individuals are automatically directed to a Web page with the instructional video and the Web-based consent form. Phase 3 individuals who are not eligible are automatically notified of their ineligibility, instructed to exit the questionnaire, and are thanked for their time.

Run-In Period

Upon consenting to participate in the study, all participants begin the 7-day run-in period to screen participants for compliance. This run-in period must be completed to qualify for randomization. Each day during the 7-day run-in period, participants receive an email with a link to a brief Web-based survey, where they complete a daily emotion report using the revised Differential Emotions Scale (DES; see [Multimedia Appendix 1](#)) [35]. Participants who complete at least four emotion reports within the first 7 days are randomized to the study. Participants who do not complete at least four emotion reports within the first week are given a second opportunity to do so. If they do not complete at least four emotion reports within the second 7-day run-in period, they are not randomized in the study. We have used this run-in period in our prior research to screen out noncompliant participants [53].

In addition to the daily emotion reports, participants also complete ecological momentary assessments (EMAs) of their positive and negative emotion [56] during the run-in period. Specifically, participants receive SMS text messages (short message service, SMS) on their mobile devices three times per day for 3 days over the course of the week, prompting them to answer questions regarding their current emotional experience. In phases 2 and 3, participants are also completing measures of their daily negative stressors (assessed using the Daily Inventory of Stressful Events, DISE) [57,58] during the run-in period. The DISE is included in the brief Web-based survey sent to participants (see [Multimedia Appendix 1](#)). Although we are collecting EMAs and DISE during the run-in period, we are not using this data to inform whether participants are randomized to the study.

Textbox 1. Eligibility criteria for participation.

Eligibility criteria

1. Be 18 years or older
2. Have daily access to the internet
3. Own a mobile phone
4. Live in the United States
5. Be fluent in the English language (reading and writing)
6. Have elevated depressive symptoms (8-item Patient Health Questionnaire, PHQ-8, depression score ≥ 5) [55]

Randomization

In phase 1, participants are randomly assigned to one of the three groups using simple randomization. In phases 2 and 3, we are stratifying randomization based on gender and level of depressive symptom severity to ensure sufficient numbers of each group within each condition. We are using the 8-item Patient Health Questionnaire (PHQ-8) [55] as our measure of depressive symptom severity. In phase 2, we are stratifying based on three levels of depressive symptom severity (PHQ-8 score: 5-9, mild; 10-14, moderate; ≥ 15 , severe) [55] and by gender. However, to be more consistent with recommended interpretations of PHQ scores [59], in phase 3, we are stratifying based on four levels of depressive symptom severity (PHQ-8 score: 5-9, mild; 10-14, moderate; 15-19, moderately severe; ≥ 20 , severe) and by gender. The randomization assignments were computer-generated via the study survey software (Qualtrics in phase 1 and Research Electronic Data Capture, REDCap in phases 2 and 3) that accounted for participants' demographic information and depressive symptom severity scores. The computer-generated randomization was performed by the study coordinator, who was not involved with either the intervention or the assessments, as both were completed online.

Assessments and Incentives

For all three pilot trials (phases 1-3), we are administering assessments at the following four time points (see Figure 1): baseline, post intervention (7 weeks post baseline), follow-up 1 (FU1; 1 month post intervention), and follow-up 2 (FU2; 3 months post intervention). The EMA text distribution and data collection are administered using PingQuest [60], a platform for the delivery and management of ecological momentary assessment data, developed by one of the authors (MC). All other assessments are administered online. In phase 1, we are using Qualtrics survey software [61] for Web-based data collection and management. In phases 2 and 3, we are using REDCap [62] for Web-based data collection and management, hosted at Northwestern University. Both Qualtrics and REDCap are secure, Health Insurance Portability and Accountability Act of 1996 compliant, Web-based apps designed to support data collection and management for research studies. Participants for all three pilot trials are compensated up to US \$60 total: US \$45 for completion of all assessments (US \$5 for baseline, US \$20 for post intervention, and US \$10 for each follow-up) and up to US \$15 for completing the first 3 weeks of daily website visits or completing the intervention [35,55,56,63].

Positive Emotion Skills Intervention

Adapting and Refining Intervention Materials

We have developed a five-session, multicomponent positive emotion skills intervention that can be administered either in person or online. In prior studies, this intervention has shown promise for reducing depressive symptoms and improving psychological adjustment in people coping with the stress of a chronic illness, including women with metastatic breast cancer [51], people newly diagnosed with HIV [54], and people with type 2 diabetes [53]. The intervention involves teaching participants eight empirically based skills to increase the frequency of positive emotion experienced in their daily lives:

(1) noticing positive events [64,65], (2) capitalizing on or savoring positive events [66,67], (3) gratitude [68,69], (4) setting and working toward attainable goals [70,71], (5) mindfulness [72,73], (6) positive reappraisal [74,75], (7) focusing on personal strengths [76,77], and (8) small acts of kindness [78,79]. At each session, participants are taught up to three of the skills and are asked to practice each skill as home practice every day until the next weekly session.

In phase 1, we adapted the existing Web-based intervention content to address the specific needs and perspectives of people with depression. First, we modified the intervention content to substitute one of the existing skills in the positive emotion skills intervention, skill # 4: setting and working toward attainable goals, with the skill of behavioral activation. Behavioral activation involves teaching participants techniques to monitor their mood and daily activities and to develop plans to increase the number of activities they engage in through activity scheduling. Behavioral activation shares similar principles as the skill of setting and working toward attainable goals; however, behavioral activation has been studied extensively in the context of depression, and there is a strong evidence base supporting the effectiveness of behavioral activation for reducing symptoms of depression [80-83]. As such, we incorporated techniques and concepts from behavioral activation into the positive emotion skills intervention.

In addition, we adapted the existing Web-based intervention content (eg, text, exercises, and images) to address the specific needs and perspectives of people with depression. Table 1 shows the original intervention content and the new material we added to ensure that our intervention is applicable and useful to individuals experiencing symptoms of depression. The new material is intended to address biases, motivational deficits, or resource limitations (eg, lack of social support) that might make it difficult for participants with elevated depressive symptoms to understand the skills or engage with the exercises.

User Testing

Materials were modified and revised in multiple cycles based on feedback from Web-based participants. Specifically, in a prior unpublished study, we collected iterative feedback from 250 Web-based participants with elevated symptoms of depression (PHQ-8 score ≥ 5) recruited from Amazon's Mechanical Turk [55]. Consistent with standards of user testing to achieve 95% power to detect text that is offensive, unclear, or otherwise problematic [84], each adapted lesson was shown to at least 20 individuals. Participants read sections of text from the adapted intervention and then completed multiple choice quizzes to assess whether they understood the core idea being presented. Testers also answered Likert-scale questions about whether they found the material enjoyable, understandable, and useful, along with open-ended questions about any material they found offensive or inapplicable. A piece of text was considered acceptable if it met three criteria: (1) at least 80.0% (16/20) of testers passed the comprehension quiz, (2) the average rating for enjoyment and usefulness was above the neutral point on the scale, and (3) no testers found the material seriously offensive or inappropriate. Material that failed these criteria was further revised according to testers' suggestions for

improvement and then resubmitted for testing by at least 10 new participants. For example, early testers viewed several lessons as overly optimistic or difficult; after rewriting these lessons, feedback in subsequent rounds of testing was substantially more positive and met criteria for acceptability.

Mobile Affect Regulation Intervention With the Goal of Lowering Depression Intervention Content

The resulting MARIGOLD intervention teaches eight positive emotion skills using lessons and homework that have been tailored to people with elevated symptoms of depression (see Table 1).

Table 1. Mobile Affect Regulation Intervention with the Goal of Lowering Depression (MARIGOLD) intervention content adapted for depression.

Session	MARIGOLD ^a intervention content
Session 1	
Skills 1 and 2: noticing and amplifying positive events; Skill 3: gratitude	<ul style="list-style-type: none"> • Learning to notice small positive moments in life and savoring or amplifying the positive emotional experience. Noticing positive events can help to reduce stress, even in the face of significant life stress • Cultivating gratitude as another way to savor positive moments. The potential for gratitude to strengthen our connections with others
Depression material	<ul style="list-style-type: none"> • Recognizing cognitive biases that can lead to discounting or failing to notice or remember positive events
Exercises	<ul style="list-style-type: none"> • Daily positive events journal. Daily gratitude journal
Session 2	
Skill 4: activation	<ul style="list-style-type: none"> • Techniques for setting goals that are appropriately challenging but feasible
Depression material	<ul style="list-style-type: none"> • Ways to practice scheduling activities to break out of a negative spiral • Added emphasis on setting small, attainable goals and working up to challenging goals gradually • How to select goals that will provide pleasure or mastery experiences
Exercises	<ul style="list-style-type: none"> • Select a goal for the week and record progress daily
Session 3	
Skill 5: mindfulness	<ul style="list-style-type: none"> • Learning to increase the enjoyment of everyday activities by training ourselves to pay attention, on purpose, in the present moment, with nonjudgment. Learning to practice mindfulness both informally and formally
Depression material	<ul style="list-style-type: none"> • Using present-focused awareness to combat rumination. Using acceptance to tolerate unpleasant situations with less negative emotion
Exercises	<ul style="list-style-type: none"> • Select an everyday activity to do mindfully (informal practice). Guided mindfulness meditations (formal practice)
Session 4	
Skill 6: positive reappraisal; Skill 7: strengths	<ul style="list-style-type: none"> • Positive reappraisal as a way to respond to everyday stressors and dispute excessively negative interpretations. Recognizing that it is possible to acknowledge a situation as negative but still appreciate potential benefits (silver linings) or mitigating factors • Recognizing personal strengths, skills, or talents
Depression material	<ul style="list-style-type: none"> • Role of negative cognitions in causing or maintaining depression. Support for acknowledging strengths even in the presence of low self-esteem
Exercises	<ul style="list-style-type: none"> • Daily reappraisal journal • Daily strengths journal (record ways a personal strength or talent was used)
Session 5	
Skill 8: acts of kindness	<ul style="list-style-type: none"> • Engaging in small acts of kindness can help promote happiness and well-being for the individual, in addition to strengthening our relationships
Depression material	<ul style="list-style-type: none"> • Small, prosocial acts that can be performed even if one is relatively socially isolated
Exercises	<ul style="list-style-type: none"> • Do something nice for someone else each day and record it in a daily kindness journal

^aMARIGOLD: Mobile Affect Regulation Intervention with the Goal of Lowering Depression.

The skills are (in the order that they are presented) as follows: (1) noticing positive events, (2) amplifying positive events, (3) gratitude, (4) behavioral activation, (5) mindfulness, (6) positive reappraisal, (7) personal strengths, and (8) acts of kindness. MARIGOLD is delivered as a self-paced, Web-based intervention arranged into five modules containing 1 to 3 skills each. Each module is designed to be completed within 1 week; however, to allow for variations in individual schedules and self-pacing, participants are given a total of 7 weeks to complete the MARIGOLD course. Participants must finish the current week's skills before the next one's become available, so the skills are taught in succession. Each skill is associated with a home practice exercise in a journal format, and participants are encouraged to spend approximately 10 min each day reviewing the skill and completing home practice. Participants may also revisit previous weeks' skills and home practice exercises. After completion of the course, participants maintain access to the course website indefinitely, allowing them to review the skills or continue with their home practice.

In addition, booster sessions that contain brief summaries of the positive emotion skills, along with encouragement and goal setting for continued practice, become available immediately after course completion. For example, if participants are going through a booster session for skill # 8: acts of kindness, they will review a brief summary the skill, as well as a few examples of random acts of kindness. They will also have the chance to review their previous journal entries for the skill and print out a bonus handout on the skill. Finally, in the booster sessions, participants have the opportunity to set a goal to enact the skill. Specifically, participants will be asked to complete the following steps: (1) set a goal for enacting the skill (ie, "I will commit to doing something nice for a friend, loved one, or stranger every day"), (2) a time frame of the commitment (1 week, 2 weeks, 1 month, or 2 months), (3) the frequency of the commitment (more than once a day, once a day, every other day etc), (4) how they plan to keep track of their commitment (write about it on the MARIGOLD website or talk to a friend or activity partner), (5) write down an encouraging note to themselves for when it gets difficult to enact the skill, and (6) digitally sign their name to a summarized page with their commitment. Following these six steps, participants will be emailed a copy of their responses as a reminder.

Outcomes

Retention and Adherence

In this study, we define retention as the number of assessment questionnaires that participants complete. In addition, we define adherence to the intervention in two ways: (1) the number of lesson modules accessed by the participant and (2) the proportion of the intervention content that participants complete (ie, the number of pages that participants view out of the total number of pages in the intervention).

Preliminary Efficacy Measures

Assessments include self-report measures of demographic and clinical characteristics, depression, positive and negative emotion, psychological well-being, coping resources, potential moderators, and satisfaction with the intervention. See

[Multimedia Appendix 1](#) for the full list of measures. The follow-up interviews in phases 1 and 2 are conducted over the telephone by research staff; if the participant is in the facilitator contact arm (phase 2 only), we ensure that the research staff conducting the follow-up interview is not the same person who was assigned as the participant's facilitator. In phase 3, the follow-up interviews are delivered as a Web-based survey.

The primary efficacy outcome in the proposed research is depressive symptom severity, which we are measuring using the PHQ-8 [55]. We will also assess the Center for Epidemiological Studies-Depression [63] as an additional measure of depressive symptomatology. Emotion is also a central construct in the proposed research. As such, we are measuring it multiple ways: (1) daily emotion reports [35], completed daily during the run-in period (which serves as the baseline measure) and during the 5- to 7-week intervention period, and also daily, in 1-week bursts at each of the three postintervention assessment periods (post intervention, FU1, and FU2); (2) past-week emotion reports [35] at each of the four assessment periods (baseline, post intervention, FU1, and FU2); and (3) EMA [56] completed three times per day for 3 days per week during the run-in period (which serves as the baseline measure) and for 1-week bursts at each subsequent assessment (post intervention, FU1, FU2).

Study Design

Phase 1: Pilot Test of the Web-Based Positive Emotion Skills Intervention Tailored for Participants With Elevated Symptoms of Depression

Participants (N=60) are randomized into one of three arms: (1) MARIGOLD intervention (N=30), (2) active control (daily emotion reporting during the 5-week intervention period; N=15), or (3) waitlist control (N=15). Participants in the intervention arm receive a five-session positive emotion skills intervention tailored for participants with elevated symptoms of depression (described above). Participants in the daily emotion reporting arm complete the DES [35] daily for the 7-week duration of the intervention period. In past research, we have established that emotion reporting is acceptable as a control condition (retention rates of approximately 80%, similar to the intervention) and that participants perceive it as being beneficial, providing some of the features of a placebo control [53]. Participants in the waitlist control group only complete the assessment questionnaires. Upon completion of the FU1 assessment, participants in both the emotion-reporting and waitlist control arms receive access to the MARIGOLD intervention. Following phase 1, we review the study feedback from telephone interview transcripts and modify and refine the study design, staff training, and intervention content accordingly.

Phase 2: Pilot Test of Three Enhancements to Increase Retention and Adherence

In phase 2, we are developing and pilot testing three enhancements that can be added to the Web-based intervention for the purpose of boosting retention and adherence among people with elevated depressive symptoms. Participants (N=75) are randomized into one of three arms, the intervention plus one enhancement: (1) intervention + facilitator contact (N=25),

(2) intervention + ODB (N=25), and (3) intervention + virtual badges (N=25). Each enhancement is designed to improve retention and adherence to the intervention by removing practical and motivational barriers to continued engagement. We describe each enhancement strategy below.

Facilitator Contact

Even when interventions are entirely computerized, contact with a person associated with the intervention has been found to increase adherence to the study [43,85-89]. Participants assigned to this enhancement arm are contacted once per week by a facilitator, who encourages them to continue with the program and answers any questions they have about the study. Contact is limited to no more than 5 min per week. The facilitator schedules a time each week to call the participant by telephone. If they cannot agree on a time or the participant cannot be reached that week, the facilitator contacts the participant by email. The content of the facilitator script is similar for both telephone and email communication. Before contacting the participant (either via telephone or email), the facilitator checks in on the participant's progress in the course (eg, the skills accessed that week, home practice completion, and daily emotion survey completion). The facilitator begins the facilitator contact (both telephone and email) by briefly summarizing to the participant their progress in the course that week. Next, facilitators check in with the participant about (1) the skills covered that week, (2) the home practice that week, (3) the daily emotion surveys, and (4) any issues with the technology. Specifically, the facilitator asks participants how each component (eg, skills covered and home practice) went that week, whether the participant experienced any challenges, difficulties, or barriers with each component that week, and whether they had any comments or questions. The facilitator contact ends with the facilitator confirming the time for next week's facilitator contact call, unless it's the final week (week 7). When facilitators email participants, facilitators encourage participants to reply with questions, comments, and technology issues. The facilitator does not offer counseling to the participant during the facilitator contact. If the participant begins to request counseling, the facilitator reminds the participant that the facilitator is not in the position to provide advice or therapy to the participant and reinforces that their role is to answer questions, help the participant progress through the course, and discuss challenges, goals, or technology issues. The facilitator encourages the participant to identify opportunities to apply the MARIGOLD skills in their daily life using language from the course content. In cases where the participant is actively seeking counseling, the facilitator recommends that the participant speak with their medical provider, and if they don't have a medical provider, the facilitator offers resources for the participant to find medical coverage (see training section below).

Online Discussion Board

Prior research has found that receiving peer support from other users via a Web-based discussion forum can increase rates of

adherence to Web-based interventions [90-94]. Participants assigned to this enhancement arm are able to share questions, experiences, and encouragement with other participants in a pseudonymous Web-based environment (ie, each participant has a consistent username, but it contains no information about their identity). Research assistants serve as moderators, checking the discussion board one or more times weekly to remove posts that are inappropriate (eg, profanity, advertisements, and bullying), to identify any concerns about participant safety or suicidality, to post prompts or suggestions to start discussions, to provide encouragement, and to answer broad questions about the study. Moderators remind users regularly and as needed about guidelines for the discussion board (eg, its supportive purpose and the importance of protecting privacy). They do not provide detailed answers to questions about the intervention or discuss individual exercise responses.

Virtual Badges










Research shows that learning tasks can be made more engaging and memorable when participants are given proximal goals and benchmarks to strive for and when their accomplishments are reinforced with rewards [95,96]. Participants assigned to this enhancement arm receive virtual flower badges for accomplishing tasks and meeting milestones. These colorful badges are collected on participants' personal green garden plot, and individuals are encouraged to grow their garden (see Figure 2). Flowers are awarded for different behaviors that can occur once or be repeatable. For example, participants can earn a blue flower each time they read a skill (repeatable) and one pink sunflower after they read all the skills (single occurrence). Completing home practice and logging into the website are also incentivized, with badges awarded for completing at least one home practice exercise for 4 consecutive days (repeatable) and logging into the website for 7 consecutive days (repeatable).

Following phase 2, we review the study feedback from participants and modify and refine the study design, staff training, enhancements, and intervention content accordingly.

Phase 3: A Multifactorial Randomized Controlled Pilot Trial to Test Each Intervention Enhancement for Retention and Adherence

Participants (N=600) are randomized to receive the basic intervention, the intervention plus one or more of the three enhancements, or an emotion-reporting only control condition. Specifically, the study is a multifactorial design in which participants are randomized into one of the following nine arms (approximately 67 per arm): (1) intervention only, (2) intervention + facilitator contact, (3) intervention + ODB, (4) intervention + virtual badges, (5) intervention + facilitator contact + ODB, (6) intervention + facilitator contact + virtual badges, (7) intervention + ODB + virtual badges, (8) intervention + facilitator contact + ODB + virtual badges, and (9) emotion reporting only control.

Figure 2. Example garden plot with virtual flower badges and accompanying key in the virtual badges enhancement.

	Creating a Profile
	Reading a Skill
	Logging in to the website for 7 consecutive days
	Completing at least 1 practice per day for 4 consecutive days
	Recording your emotions ("FEEL") at least 4 times over the past week
	Reading all of the Skills
	Completing the Post Intervention Survey Booster
	Completing the 1 Month Survey Booster
	Completing the 3 Month Survey Booster

Training, Fidelity, and Protection of Human Subjects

All staff members receive training on the overall study design and procedures relevant to their staff assignment, including (1) The technology for participant tracking and data collection (eg, REDCap, Qualtrics, and PingQuest); (2) Procedures for serving as a facilitator in the facilitator contact enhancement (eg, training on scheduling telephone and email correspondence with participants, conducting the brief facilitator telephone calls using a standardized facilitator script (see above) to ensure consistent delivery of facilitator contact); (3) Procedures for serving as a moderator of the ODB; (4) Training on the booster sessions; and (5) Protocol for responding to participant suicidality or distress.

Facilitators are trained on how to handle cases of extreme distress or suicidality expressed over the telephone, via email, or on the ODB. In cases of extreme distress or suicidality, the research staff is trained to emphasize to the participant that MARIGOLD is not therapy and to tell participants to contact 911 in the case of an emergency. As part of the distress-suicidality protocol developed by one of the authors (EA), any signs of distress, however small, is reviewed

collaboratively by the facilitator, EA, and the study coordinator (ES) to monitor the safety and well-being of participants and to respond appropriately. Facilitators do not offer medical advice and instead, encourage participants to consult their medical provider, offer resources to find a medical provider if he or she does not have one, and provide relevant resources to participants (eg, a suicide hotline).

Training sessions are conducted initially during the study start-up and when onboarding new staff members, on an ongoing basis as the study protocol is updated across the three phases, and on an as-needed basis to address individual cases and procedural issues. All staff members maintained updated Human Subjects Research training either through Collaborative Institutional Training Initiative or the National Institutes of Health (NIH) Human Subjects Research module.

Planned Analyses

In all three phases of the study, we plan to conduct intention-to-treat analyses to examine (1) Retention and adherence to the intervention and (2) Preliminary efficacy of the intervention. In phase 3, we will have sufficient power to conduct additional analyses examining (3) Moderators of

retention and adherence within each randomization arm, (4) Moderators of the primary and secondary efficacy outcomes within each randomization arm, and (5) Whether intervention effects are mediated by increases in positive emotion.

Retention and Adherence

Retention will be defined as completing the baseline, postintervention, and follow-up assessments. We will categorize retention at each assessment as a binary outcome and will test for differences in the proportions of participants who are retained at each assessment using a binary logistic regression model using dummy variables to represent each arm. Adherence will be assessed in intervention participants only and measured in two ways: (1) the number of skills accessed and (2) the proportion of the intervention completed (ie, the number of pages viewed out of the total possible pages across all lesson modules in the intervention). In the phase 1 pilot, we will report descriptive statistics of adherence in the intervention arm and will explore whether retention differs as a function of arm (intervention vs emotion-reporting control vs waitlist control) using a binary logistic regression, with dummy variables to represent each arm. In the phase 2 pilot, we will explore whether retention and adherence differ as a function of enhancement type using a binary logistic regression for retention and linear regressions for adherence, with dummy variables to represent each arm. In the phase 3 pilot, we will use additional contrast tests to explore whether retention and adherence differ as a function of enhancement type received (no enhancement, facilitator contact, virtual badges, or ODB), as well as whether receiving certain combinations of enhancements offers additional benefits for increasing retention and adherence.

Preliminary Efficacy

Although this investigation is mainly focused on optimizing adherence and retention to the intervention, we will conduct analyses examining the preliminary efficacy of the intervention. Our primary measures of preliminary efficacy will be depressive symptom severity, as assessed by the PHQ-8 [55]. We will also assess change in positive and negative emotion and other indicators of psychological adjustment (eg, perceived stress and meaning and purpose) as secondary outcomes.

For each outcome, we will estimate growth curves within a multilevel modeling (MLM) framework [97] to assess change in each outcome across the four assessment points (baseline, post intervention, FU1, and FU2). MLM offers an approach that accommodates missing data points and nonindependence in observations. We plan to model time at level 1 and randomization arm at level 2 using dummy variables to represent each arm. In phase 1, the primary parameters of interest will be the differences in the magnitude of change in preliminary efficacy outcomes between the intervention arm and each of the control arms over time. In phase 2, the primary parameters of interest will be the magnitude of change in outcomes across all three randomization arms over time. In phase 2, we will also explore whether the three enhancement arms (facilitator contact, ODB, and virtual badges) differ in their magnitude of change in preliminary efficacy outcomes over time. In phase 3, the primary parameter of interest will be the difference in the magnitude of change in preliminary efficacy outcomes over

time for the arms that received the intervention relative to the emotion-reporting control. In phase 3, we will also explore whether there are differences in the magnitude of change in outcomes over time as a function of enhancement type (no enhancement, facilitator contact, ODB, or virtual badges), as well as whether receiving certain combinations of enhancements may influence magnitude of change in outcomes over time. We will use significance tests comparing the information criteria of different models to determine which covariates to include in the final model.

Moderators of Retention and Adherence

In phase 3, we will assess baseline depressive symptom severity, gender, race or ethnicity, and comfort with technology as moderators of retention and adherence. This will allow us to detect whether certain enhancements to the intervention increase adherence or retention for some subpopulations but not others. For each potential moderator, we will rerun the binary logistic regression analyses with a set of interaction variables between the moderator and the dummy condition variables. Due to power limitations, we will not test all four moderators in the same model or explore any interactions among the moderators.

Mediational Analyses

Finally, in phase 3, we will test whether positive emotion mediates any effect of the intervention on overall depressive symptoms. For the mediational analyses, we will combine intervention arms to explore the effects of intervention (regardless of enhancement type). We plan to conduct multilevel moderated mediation analyses [98] using a multilevel structural equation modeling (MSEM) framework [99]. More specifically, mediation effects will be estimated by examining the indirect effect of the intervention on change in depressive symptom severity through the effect of change in the positive emotion. We will test the significance of the specific indirect effect in the MSEM model using the Monte Carlo method with 20,000 bootstraps [100,101]. In addition, we will conduct exploratory multilevel moderated mediational analyses to explore whether improvements in positive emotion mediate the intervention effects on secondary outcomes (eg, psychological well-being, perceived stress, and meaning and purpose).

Results

The project was funded in August 2014, and data collection was completed in May 2018. Data analysis is currently under way, and the first results are expected to be submitted for publication in 2018.

Discussion

Principal Findings

This paper describes the study protocol for the development and pilot testing of MARIGOLD, a Web-based positive emotion skills intervention adapted for individuals with elevated depressive symptomatology. In this work, we are tailoring the intervention content to meet the needs and challenges of individuals with elevated symptoms of depression and are pilot testing the tailored version of the intervention along with three

enhancements aimed at boosting retention and adherence to the Web-based intervention content: facilitator contact, ODB, and virtual badges. Ultimately, the goal of this research is to develop an optimized package of relevant content and retention and adherence strategies for individuals with elevated depression.

Strengths and Limitations

There are a number of strengths to this work. One strength is its innovative focus on positive emotion. Although most psychological interventions for depression tend to target the reduction of negative emotions, this intervention targets increasing positive emotion, which may be an especially promising pathway for helping individuals with elevated depressive symptoms. Another strength of this work is its focus on developing tailored intervention content and enhancement strategies that specifically address the depression-related motivational deficits that can lead to poor adherence and retention. A third strength of this work is systematic development and testing of the intervention over three phases: the development and pilot testing of the intervention content (phase 1), the development and pilot testing of the three enhancement strategies (phase 2), and a multifactorial RCT, systematically testing each enhancement strategy, alone and in combination (phase 3). A fourth strength of this work is the Web-based delivery of the intervention. If the intervention is found to be effective, the self-guided, Web-based delivery of the intervention offers the potential for low-cost, widespread dissemination of the intervention over the internet.

Despite these strengths, potential limitations of this study design should be acknowledged. One significant challenge that faces our project is the potential for our enhancement strategies to actually reduce adherence or efficacy for some users. For example, individuals who are less comfortable or experienced with technology may have difficulty accessing or utilizing the enhancements (eg, their virtual garden plot and ODB). In addition, another limitation is that our follow-up assessments are conducted relatively close to the intervention, with the final follow-up assessment at 3 months post intervention. Future research should include longer follow-up assessments (eg, 1

year post intervention), so that we may examine whether the effects of the intervention persist over an extended period of time.

Furthermore, individuals who have more severe symptoms of depression may be reluctant to engage in Web-based social interactions. We are collecting extensive quantitative and qualitative feedback regarding the intervention content and enhancement strategies, which will give us the opportunity to address any issues that participants may have regarding the accessibility and user-friendliness of the Web-based platform and to remedy any off-putting content or features of the intervention. Additionally, detecting potential moderators of the intervention (eg, comfort with technology and baseline depression severity) will be valuable in itself. Learning more about which intervention features work for which participants will contribute to the development of more sophisticated and targeted interventions in the future.

Finally, research that focuses on the benefits of increasing positive emotion can sometimes be misunderstood as minimizing the significance of depression and its harmful individual and societal consequences. This is not our intent. On the contrary, we understand that depression is real, complex, and painful. We are not encouraging people to simply adopt a *don't worry-be happy* attitude, nor do we proclaim that increasing positive emotion is a panacea. However, a growing body of evidence demonstrates that increasing positive emotion can promote psychological and physical benefits and catalyze an upward trajectory for people who experience depression or other hardships.

Conclusions

In sum, the goal of this investigation is to develop and test a Web-based positive emotion skills intervention, tailored for individuals living with elevated depressive symptoms (MARIGOLD). If this intervention proves to be effective, it can provide a cost-effective, anonymous, and flexible approach for reducing depressive symptoms and improving psychological adjustment in individuals living with elevated symptoms of depression.

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Authors' Contributions

JTM, MAC, YL, and LRS initiated, conceptualized, and designed phases 1 to 3 of the study protocol. MAC and LRS coordinated the study at UCSF. EWS coordinated the study at Northwestern. All authors assisted with the development of the study and finalized the study protocol. EOC, ELA, SMB, EWS, and SAS developed the first draft of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Study measures and administration frequency.

[PDF File (Adobe PDF File), 114KB - [resprot_v7i6e10494_app1.pdf](#)]

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Abbreviations

DES: Differential Emotions Scale

DISE: Daily Inventory of Stressful Events

EMA: ecological momentary assessment

FU: follow-up

MARIGOLD: Mobile Affect Regulation Intervention with the Goal of Lowering Depression

MLM: multilevel modeling

MSEM: multilevel structural equation modeling

NIH: National Institutes of Health

ODB: Online discussion board

PHQ-8: 8-item Patient Health Questionnaire

RCT: randomized controlled trial

REDCap: Research Electronic Data Capture

UCSF: University of California, San Francisco

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Protocol

Enhancing Executive Functions Among Dutch Elementary School Children Using the Train Your Mind Program: Protocol for a Cluster Randomized Trial

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Abstract

Background: Executive functions are higher cognitive control functions, which are essential to physical and psychological well-being, academic performance, and healthy social relationships. Executive functions can be trained, albeit without broad transfer, to this date. Broad transfer entails the translation of improved cognitive functions to daily life (behaviors). The intervention Train your Mind was designed to train executive functions among elementary school children aged 9 to 11 years, and obtain broad transfer in terms of enhanced physical activity, healthy eating, and socioemotional regulation.

Objective: This paper aims to describe the cluster randomized trial to test the effectiveness of the Train your Mind intervention.

Methods: Train your Mind was integrated into the existing school curriculum for 8 months (25 weeks excluding holidays). The effectiveness of the intervention was tested in a cluster randomized trial comprising 13 schools, 34 groups (school classes), and 800 children, using a battery of 6 computer tasks at pre- and postmeasurement. Each of the 3 core executive functions was measured by 2 tasks (Flanker and Go/No-Go; N-Back and Running Span; Attention Switching Task and Dots/Triangles). Moreover, we administered questionnaires that measure emotion-regulation, cognitive errors, physical activity, dietary habits, and the psycho-social determinants of diet and physical activity. Body mass index was also measured. Multilevel analyses will account for clustering at the school and group levels, and randomization took place at the school level.

Results: Results are currently being analyzed.

Conclusions: The main purpose of this study is to test Train your Mind's effectiveness in enhancing executive functions. Second, we investigate whether increased executive functions lead to improved physical activity and healthy eating. If found effective, executive function training could easily be integrated into school curricula everywhere, and as such, boost health, academic performance, and emotion-regulation of elementary school children, in a cost-effective manner.

Trial Registration: Netherlands Trial Register NTR5804; <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5804> (Archived by WebCite at <http://www.webcitation.org/6z9twosJ8>)

Registered Report Identifier: RR1-10.2196/7908

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KEYWORDS

executive function; children; socioemotional development, cognitive development; academic performance; physical activity; healthy eating; eHealth

Introduction

Background

Executive functions (EFs) are higher mental control functions, consisting of impulse control, working memory and cognitive flexibility [1,2]. EFs are vital to a myriad of areas in life, including physical [3,4] and psychological well-being [5], academic performance [6], and healthy social relationships [7]. EFs can be trained [8,9]. However, such strengthened cognitive functions have, as of yet, not been accompanied by meaningful, behavioral improvements in daily life—otherwise known as broad transfer [10,11]. Recent literature suggests (combining) multiple approaches to train EFs and subsequently attain broad transfer [2,10]. Train your Mind (TyM) follows these recommendations, and as such, applies 3 main modules to train EFs: (1) focused physical activity, (2) cognitive games, and (3) socioemotional development. A fourth module, (4) tailored feedback (eHealth), aims to directly change the behaviors physical activity and healthy eating. These modules are presented in great depth in a separate paper, including the development and implementation (J Bervoets et al, unpublished data, 2018). An extensive background on what EFs are, how they can be trained, and why they are so pivotal to a healthy and successful life is described in the same separate paper (J Bervoets et al, unpublished data, 2018). This paper focuses on the study design and outcome measures.

Aims and Hypotheses

This study's main objective is to enhance EFs, among 9- to 11-year-old elementary school children, through a multimodule intervention combining physical, cognitive, and socioemotional approaches. Longitudinal EF studies have revealed a substantial amount of positive correlates, including physical and mental well-being, level of education, job income, marital harmony, substance use, unsafe sex, risky driving, eating, and social relations [2,4,5]. This lead us to expect improved EFs to translate into healthier behavior in daily life (especially considering our multidimensional, integrated intervention), more specifically, in our target population. As a result of stronger EFs, we expected the children to be physically more active and eat more healthily. Such daily life improvements as a result of strengthened EFs would constitute the much-desired broad transfer. This broad transfer is hypothesized to be mediated by EFs. To bridge the seemingly distant cognitive control functions with physical activity and eating, it may help to consider self-regulation, concentration, and attention. It is easier to envision how the latter are improved as a result of stronger EFs (eg, inhibitory control can shut out distracting stimuli, keeping the mental working space clear, but also maintaining optimal levels of emotional and cognitive arousal, by self-regulation). In sum, the model we are working with assumes a 3-level cascade effect: (1) increased EFs will lead to (2) improved self-control, emotion-regulation, and attention, which in turn will facilitate (3) healthy eating and physical activity.

Main Hypothesis

The main hypothesis is as follows:

- EFs are enhanced through a multi-dimensional intervention (TyM).

Secondary Hypotheses

The secondary hypotheses are as follows:

TyM effects transfer to improved:

- Emotional-regulation
- Concentration/attention

TyM effects translate to other aspects of daily life, specifically:

- More physical activity
- Healthier dietary habits
- Reduced social/emotional/behavioral problems
- Better school performance
- These broad transfer effects are mediated by stronger EFs

Methods

Trial Design

The effectiveness of TyM was investigated in a cluster randomized trial comprising 13 elementary schools, with a total of 34 groups and 800 children. Schools in the control condition continued their regular school curriculum, and would receive the program, or any components thereof, after the third and final measurement (follow-up) had been completed. In this sense, it was a passive control group (though the same amount of time will be spent on similar activities, gym sessions, etc, minus the explicit EF training). All groups of the Dutch sixth and seventh grade of schools in the experimental condition followed the entire TyM intervention for 8 months (25 weeks excluding holidays). This means it is nearly impossible to determine effectiveness per component—our study was set up primarily to answer the question: Can EFs be enhanced through a multi-dimensional training program? If satisfactory results are obtained, TyM can be disentangled in the future to further scrutinize each component separately. Children were to be measured at 3 different time points: preintervention, postintervention, and at follow-up 6 months later. However, the follow-up could not be organized due to financial constraints.

Participants and Procedure

The promising potential that lies in training EFs (academic performance, healthy behaviors, better social relations) was presented to education foundations (Movare and Innovo) in South-Limburg, The Netherlands. Interested school directors and teachers further inquired about the willingness of other teachers to participate. A total of 13 schools, 34 groups, representing 800 pupils, decided to participate in TyM. Every sixth or seventh grade pupil (aged 9-11 years) of a participating school automatically took part in the intervention activities, as they were integrated in the existing school curriculum. Participation in measurements, on the other hand, could be refused by parents. Every child of the relevant school classes was welcome to join; we assumed normally distributed groups in terms of attention problems and fluid intelligence.

Ethics and Consent to Participate

Consent was obtained from the schools. Both parents and children were informed about the intervention and measurements, and both parents (written) and children (verbal) were asked to provide consent. Parents and students can withdraw from participation at any time. This intervention, along with the study methods and consent procedure, were approved by the Ethical Review Committee of the Faculty of Psychology and Neuroscience, Maastricht University, the Netherlands (dd. 13-08-2015, ERC PN-06-06-2015).

Availability of Data and Materials

Data are not yet available. Materials can freely be requested from j.bervoets@maastrichtuniversity.nl.

Randomization

Schools, matched by number of pupils in the participating grades, and from similar areas, were randomly assigned to either an experimental or a control condition, by means of a coin toss (simple randomization) performed by the first author of this paper. Before this process, however, 3 schools had to be assigned a condition because they would not participate otherwise. One school could only participate as a control school because they had large infrastructure works scheduled for the school year and did not want to overly burden the teachers in that hectic period. Two schools were so interested in training EFs they would only agree to participate as experimental schools, as they wanted to train EFs regardless (they could not guarantee respecting the terms of being a control school). We decided to include all the 3 schools anyway, because in any case, it would offer us valuable insights in how our novel and ambitious intervention would work in the field, especially at highly motivated schools. Because it had not yet been (sufficiently) proven in previous studies that EFs can be trained, we decided to maximize our chances of finding an answer to the most fundamental research question of our project: can EFs be trained? (by TyM). Furthermore, all schools were highly motivated to participate. This flaw in the randomization process will be taken into account during analysis.

Intervention

TyM combines (1) focused physical activity, (2) cognitive games, and (3) socioemotional development in an attempt to enhance EFs. Physical activity and healthy eating are directly targeted in a fourth module (4) tailored feedback (eHealth). To this date, it has proven challenging to sustainably train EFs, and even more so to achieve broad transfer [10]. Leading experts in the field suggest considering novel angles such as the mind-body connection and socioemotional balance [2,10,12-15]. The development, implementation, and content of these modules are described in great detail in a separate paper (J Bervoets et al, unpublished data, 2018). A brief description of the intervention is presented in the following paragraphs.

Promising results with regard to training EFs were found by a yoga [15] and a taekwondo intervention [13,14]. For TyM, core elements of kung fu were comprised into the focused physical activity component, as the fundamental idea of kung fu is self-control (achieved through rigorous training aimed at intrapersonal progress—it is by nature not competitive). After

initial workshops (for teachers) and introductory lessons (from our kung fu expert to the participating class groups), teachers lead the kung fu sessions themselves, during physical education hours at school (1 hour/week), supported by a teaching manual.

Despite an apparent lack of groundbreaking results for cognitive training within the field of EF training [2,10,16], we reasoned that this angle still merited a place in our multidimensional intervention. The idea was that effects of singular components could multiply synergistically in an integrated whole. Moreover, approaches could be combined in applications, such as cognitive and socioemotional training while playing board games (handle losing, cheating). The TyM collective cognitive games included (1 hour/week): SET, charades, taboo, and memory. Theoretically, the most appropriate games for EF training are challenging and engage multiple EF subcomponents simultaneously [2,8] (eg, SET).

Furthermore, to ensure an incremental challenge at the individual level, individual Web-based games were presented (Cambridge Brain Sciences), including adapted Raven's progressive matrices, Stroop, paired-associate learning, Hampshire tree task, and spatial working memory/planning.

An effective guide to address socioemotional development while training EFs was found in MindUp [17], in which children learn to recognize and handle emotions in a more functional way [18,19]. The core technique of mindful breathing aids children in finding and maintaining their composure. Pupils learn more about the relationships between thoughts, emotions, and behavior. We adapted the existing MindUp program to our own Dutch target population. All schools already had some kind of socioemotional development program (and allotted weekly time slot), which was replaced by our unified version of MindUp (30 minutes/week for the duration of the trial (25 weeks, excluding holidays), including what we believed were essential components (such as mindful breathing). A teaching manual with additional background information, suggested lesson structures, and hints supported the teachers for these sessions.

The latter 3 modules target EF training, whereas our fourth TyM module aims to change behavior directly; personalized feedback/advice regarding physical activity and healthy eating is generated based on psycho-social determinants that are assessed in the Web-based eHealth module. The feedback is construed through behavior change models such as Reasoned Action Approach [20] and Theory of Planned Behavior [21].

Control groups continued their regular curricula.

Primary Outcomes

At the core of our intervention and study lied EFs. These EFs were measured using a computerized task battery consisting of 6 tasks (2 per EF subcomponent), consistent with most recent suggestions from the field [2,22,23]. Careful attention was paid to the fact that testing and training tasks must be adequately different, so as to avoid practice effects (ie, merely measuring children's improvement on 1 [near-] similar task that they have repeated/practiced over and over).

In terms of the measurements themselves, we hoped that any practice effects would be minimized by the long periods of time

in between pre, post, and follow-up measurements (7 and 6 months, respectively), by the fact that there was a control group and, most importantly, by the fact that the measurement tasks were sufficiently different from the (Web-based) cognitive training tasks. Both original tasks and adapted versions of existing tasks were included in this task battery. The entire battery was pilot-tested in a small study investigating the effectiveness of a 6-session kung fu intervention designed to enhance EFs. As a result, the task battery was fine-tuned and any final glitches were ironed out; it takes about 1 hour and 15 min to complete it the first time. In the section below, we provide an overview and descriptions of the tasks per EF subcomponent.

Secondary Outcomes

As the development of EFs is boosted, we hypothesize various daily life behaviors to benefit from this as well (see secondary hypotheses for an overview of the aspects this study focused on). These outcomes constitute the aforementioned broad transfer and practical relevance of increased EFs; other than stronger EFs, what are the potential benefits for the individual? The case for physical activity and healthy eating is peculiar, as they can not only be affected by increased EFs but also by the tailored feedback eHealth module, which specifically targets these 2 behaviors.

The eHealth module operates a behavior change model that is almost entirely driven by determinants (of the targeted behaviors), assisted by additional behavior change techniques such as coping plans. These determinants are measured by the program, during the intervention, as personalized feedback is offered to the individual, in response to these determinants and how they evolve over time. However, the very same determinants are also included in the large pre and

post-intervention measurements, to allow for comparison with the control group. Measuring these determinants allows us to investigate what changes in determinants drove the change in behavior—useful knowledge in light of similar future behavior change interventions. An overview of the outcome measures is presented in [Textbox 1](#).

Executive Functions Battery

- Inhibitory/interference control: (1) Flanker and (2) Go/No-Go
- Working memory/updating: (3) N-Back and (4) Running Span
- Cognitive flexibility/switching: (5) Attention Switching Task (AST) and (6) Dots/Triangles

Stimulus acquisition and presentation in all 6 tasks are controlled by Presentation software. Response button boxes (Cedrus RB-844), connected to 30 identical Hewlett-Packard laptops, registered responses very accurately.

Flanker Task

The current task battery makes use of an adapted version of the original Eriksen Flanker task [24] to measure children's response interference control abilities. In this adapted version, letters are used instead of arrows to avoid the well-documented developmental ceiling effects associated with the traditional arrow flanker task, which is found at around 10 years of age in normally developing children [25].

An array of 3 letters is presented at the center of the screen. The middle letter is the target letter and the other 2 are flankers. Participants are instructed to press the left button on the Cedrus RB-844 response button box when the target letter is a B or H, and the right button if the target is letter F or T—while ignoring the flanking stimuli (two B's, H's, F's, or T's).

Textbox 1. Textbox 1. Overview of the outcome measures.

<p>Primary Outcomes</p> <ul style="list-style-type: none"> • Executive functions: Computer task battery <ul style="list-style-type: none"> • Working memory: N-Back; Running Span • Impulse control: Flanker; Go/No-Go • Cognitive flexibility: Attention switching task; Dots/triangles <p>Secondary Outcomes</p> <ul style="list-style-type: none"> • Emotion-regulation, attention, healthy behaviors: Survey <ul style="list-style-type: none"> • Emotion-regulation: FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen; Questionnaire for the Assessment of Emotion Regulation among Children and Adolescents) • Mental health—social/emotional/behavioral functioning: Strengths and Difficulties Questionnaire • Attention-Related Cognitive Errors (Scale; ARCES) • Physical Activity Questionnaire (PAQ-C) • Dietary habits • Determinants of dietary habits and physical activity • Demographics • Additional data from provincial database: socioeconomic status and academic performance (CITO; Centraal Instituut voor Toetsontwikkeling; Central Institute for the Development of Tests; a standardized test of academic performance, widely used in the Netherlands)

There are 3 stimulus conditions:

1. Stimulus-response congruent (C) condition: no response conflict (eg, B B B)
2. Stimulus incongruent (SI) condition: target and flankers are different letters but both are mapped to a response of the same hand so that there is stimulus conflict but no response conflict (B H B; H B H; F T F; T F T)
3. Stimulus and response incongruent (SRI) condition in which the flankers and target differ in both the physical appearance (stimulus conflict) and the required response hand (response conflict; eg, F B F; H T H).

A total number of 144 trials are presented in 3 blocks of 48 trials. Each of the 3 conditions is randomly presented with equal probability within task blocks. Each trial starts with the presentation of 2 flanking stimuli for 200 ms (to establish flanker priming effects), after which the middle target letter appears and the entire array of 3 letters stays on the screen for 700 ms, followed by a fixed interstimulus interval (ISI) of 500 ms, during which a fixation cross is presented. The maximum response window is 1400 ms. The experimental task (no feedback) is preceded by a practice block of 18 trials in which the feedback: “correct,” “wrong,” or “faster” is given. To measure the executive function *response interference control* the accuracy and reaction time of participants in the C and SRI conditions will be compared.

Go/No-Go

In the current Go/No-Go task, the participants are presented with a random series of letters drawn from the alphabet and appearing one by one in the center of the computer screen. The participants’ task is to respond to every letter by pressing the right button on a Cedrus RB-844 response box (Go stimuli), but to refrain from responding when they see the letter X (the No-Go stimulus). Each trial lasts 1200 ms, with a stimulus presentation rate of 500 ms and a fixed ISI of 700 ms. A total of 200 trials are presented in 2 blocks of 100, with a pause in between. Within each task, the probability that a No-Go stimulus will appear is 10.0% (main task: twice 10/100). The experimental task (no feedback) is preceded by a text instruction screen and 15 practice trials (feedback is only given when a participant incorrectly responds to the No-Go stimulus). The Go/No-Go task has been widely used to study the development of response inhibition [26].

N-Back

This version of the N-back task has been used to investigate the development of nonspatial working memory capacity among children and adolescents [27]. Semirandom sequences of letters (A, B, F, G, H, K, L, S, T, W, X, Z) appear one at a time in the center of the screen. Letters (height: 1 cm, width: 0.5 cm) are black and presented between 2 black vertical bars (height: 1.5 cm) on a gray background. The current N-back task consists of 1- and 2-back conditions. Participants are instructed to respond by pressing a Cedrus button box RB-844, with their right index finger, whenever they detect a target event. In 1- and 2-back conditions a target is, respectively, defined as a letter that is identical to the letter presented 1 (eg, T-T), or 2 trials back in the sequence (eg, A-B-A). The experimental task consists of a total of 200 trials, presented in 4 blocks of 50 stimuli, 2 blocks

per condition. The order of the block presentation is: 1-back – 2-back – 1-back – 2-back. All blocks have an identical target frequency of 36% (18/50). Each trial lasts 2000 milliseconds (ms) with a stimulus duration of 500 ms and a fixed ISI of 1500 ms. The experimental tasks are preceded by several instruction screens with pictures explaining the specific task requirements, directly followed by 20 practice trials (target event frequency 40%, 8/20) during which feedback is given (“wrong” for false alarms and “missed” when a target-event is not detected). Due to the complexity of the 2-back blocks, a second practice session of 20 trials is automatically run when the success rate in the first practice block falls below 70% (14/20). No feedback is given during the experimental/real tasks.

Running Span Task

In this task, a series of numbers varying in length are presented one by one at the center of the computer screen. Each number series is preceded by “The next rows of numbers will follow. If you are ready, press ENTER,” after which the series starts. Within a series, each digit is presented for 1 s with an interval of 500 ms between them. Following the presentation of the entire sequence, participants are presented with a screen showing the presented sequence with the last 3 numbers displayed as 3 question marks. The participants have to recall these 3 missing numbers from working memory and type them in the spaces indicated by the question marks by using the number buttons on the laptop keyboard and ENTER when finished. For example: if series 4, 2, 5, 8, 3, and 9 is presented, the participant sees “4 2 5 ? ? ?” on the screen and has to enter 8, 3, 9 in the spaces represented by the question marks.

In the present task, 12 number series are presented that differ in length; there are 4 series each of 5, 6, and 7 digits that are presented randomly so that participants cannot predict series length. In each case, the last 3 digits of a series have to be recalled. The experimental part of the task—during which no feedback is given—is preceded by instruction screens explaining the task followed by 2 practice trials with feedback. The dependent measures in this task are the mean percentage of correctly completed trials per series length and the average time at which the enter button is pressed once the missing numbers are entered. A similar version of this running span, the digit memory task, has been used before to measure updating in children [28].

Attention Switching Task (AST)

The present task is an adapted version of the task previously used in 2 developmental studies by Cepeda et al [29,30]. The task consists of 3 blocks: 2 nonswitch blocks (2 x 32 trials) precede 1 switch block (64 trials). On each trial, 1 of the 4 possible stimulus displays is presented (1, 111, 3, or 333). In the first block, the instruction “which number?” precedes the stimulus 1 or 111 and is correctly responded to by pressing the left button on the Cedrus RB-844 button box (and right button for 3 or 333). In the second block (“how many numbers?”), the left response button represents the single digits (1 and 3), whereas the right button is associated with a string of 3 digits (111 or 333), irrespective of the identity of the digits. In the third block (the switch block), cue instructions (“which number?” or “how many numbers?”) alternate randomly,

meaning that participants have to switch between instructions on about half of the trials. Every trial starts with the presentation of the cue, followed by the stimulus after 200 ms. Both remain on the screen until a response is given. Each experimental block commences with instruction screens explaining the task and allowing the participants to practice each stimulus-response configuration. Feedback is given during the entire task (“wrong” or “faster,” no feedback for correct responses).

Dots/Triangles

This task is adapted from the original [22] in several ways: (i) Diagram instruction screens have been inserted, (ii) feedback is given after every trial during the practice period (for 1000 ms) rather than after the entire block, (iii) no feedback is given during the experimental blocks, (iv) a minimum for the difference between the amounts of dots and triangles is set at 2, (v) the entire task has been shortened, (vi) in the third and last block, rules switch every 3 trials (instead of every 4 trials). Blocks 1 and 2 are nonswitch and consist of 30 trials (preceded by 5 practice trials). The third block (switch) consists of 93 trials (63 non-switch and 30 switch) and is preceded by 15 practice trials. Every trial starts with a blank screen for 1000 ms, followed by an empty 4 x 4 grid presented for 1000 ms, after which the dots or triangles appear and remain visible until a response is given. Feedback is only given during practice trials (“correct,” “wrong,” and “too fast”), and appears for 500 ms directly after a response is given, before the next empty grid is presented. The ISI duration in practice and experimental trials is the same, as feedback is given during the ISI interval (500 ms). A previous study with 7- and 11-year-old children identified a relatively early maturation mechanism associated with task-set inertia and a later maturing mechanism relating to task-set reconfiguration [31]. Figure 1 shows how the testing

laptops and response button boxes are best setup at the elementary school.

Questionnaires

Children

In addition to EFs, we were also interested in more behavioral outcomes, for which we compiled a Web-based questionnaire (pilot-tested: 1 hour to complete) comprising:

Feel-KJ

This questionnaire measures 15 (mal)adaptive emotion regulation strategies in relation to anxiety, sadness, and anger: (1) Problem Solving (eg, “I try to change what makes me angry”), (2) Distraction (eg, *when I am sad...* “I do something fun”), (3) Forgetting (eg, “I try to forget what makes me angry”), (4) Acceptance (eg, “I make the best of it”), (5) Humor Enhancement (eg, “I think about things that make me happy”), (6) Cognitive Problem Solving (eg, “I think about how I can solve the problem”), (7) Reevaluation (eg, “I tell myself it is nothing important”), (8) Giving Up (eg, “I don’t want to do anything”), (9) Withdrawal (eg, “I don’t want to see anyone”), (10) Rumination (eg, “I cannot get it out of my head”), (11) Self-Devaluation (eg, “I blame myself”), (12) Aggressive Actions (eg, “I get into a quarrel with others”), (13) Social Support (eg, “I tell someone how I am doing”), (14) Expression (eg, “I express my sadness”), and (15) Emotional Control (eg, “I keep my feelings to myself”). There is a total of 90 items (2 items x 15 strategies x 3 emotions). In a previous research, exploratory factor analysis has suggested that the first 7 (1-7) strategies can be classified as Adaptive Emotion Regulation, the next 6 (8-13) as Maladaptive, and that the remaining Social Support, Expression, and Emotional Control strategies could not be classified as Adaptive or Maladaptive Emotion Regulation [32].

Figure 1. Example of an executive function (EF) testing station setup at an elementary school.



Internal consistency has repeatedly been found to be high, also among children [33]. We included the Dutch version [33] of the FEEL-KJ to be used in our outcome measurement.

Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a behavioral screening questionnaire that assesses 3 domains of children's overall mental health: social, emotional, and behavioral functioning [34]. A total of 25 items are evenly distributed among 5 scales: (1) Conduct Problems (eg, lying and stealing: "I am often accused of lying or cheating"), (2) Inattention Hyperactivity (eg, impulsivity and concentration problems: "I am easily distracted"), (3) Emotional Problems (eg, unhappy mood and worries: "I am often unhappy, down-hearted or tearful"), (4) Peer Problems (eg, being bullied: "Other children or young people pick on me or bully me"), and (5) Prosocial Behavior (eg, sharing and being helpful: "I am helpful when someone is hurt, upset or feeling ill"). Items are rated on a 3-point Likert Scale, with 0 representing "not true," 1 representing "somewhat true," and 2 representing "certainly true." Several items are reverse-scored. The first 4 subscales summed up together give a total difficulty score ranging from 0 to 40, with a higher score indicating more difficulties. The Prosocial Behavior subscale reflects the strengths of the individual. The SDQ is an internationally approved instrument of value due to its brevity and psychometric properties [35]. In terms of internal consistency, one study among 7- to 15-year-old Finnish children and adolescents reported a Cronbach alpha of .71 [36]. We included the Dutch version of the SDQ [37] to be used in our outcome measurement.

Attention-Related Cognitive Errors Scale (ARCES)

The ARCES consists of 12 questions measuring everyday mistakes as a result of not paying sufficient attention to the task at hand, also called mind-wandering [38]. Example questions include: "I make mistakes because I am doing one thing and thinking about another" and "I fail to see what I am looking for even though I am looking right at it." The 12 items are rated on a 5-point Likert Scale ranging from 1 representing "never" to 5 representing "very often." A mean score is computed for each individual by summing the scores of all questions. The ARCES has been rigorously validated and normed [38]. We included a back-translated Dutch version of the ARCES, with some questions adapted to make them suitable for children, to be used in our outcome measurement.

Physical Activity Questionnaire-Child (PAQ-C)

The PAQ-C is an instrument used to assess self-reported levels of physical activity during the past 7 days for 8- to 14-year-old students [39]. The PAQ-C provides a summary physical activity score derived from 9 items, each scored on a 5-point scale. Examples include: "In the last 7 days, during your physical education (PE) classes, how often were you very active (playing hard, running, jumping, throwing)? Response options (check one only) are: "I don't do PE," "hardly ever," "sometimes," "quite often," "always." Or, "In the last 7 days, how many evenings did you do sports, dance, or play games in a very active way?" Response options are (check one only) "none," "1 time last week," "2 or 3 times last week," "4 or 5 times last week," "6 or 7 times last week." The scale concludes with a small agenda (7 week days) on which the child marks how often he

or she did physical activity for each day last week ("none" to "very often"). Excellent content validity, acceptable interitem reliability and a moderate to good strength of interrater agreement has been found for the Dutch PAQ-C [40].

Dietary Habits

The same eating behaviors as were addressed in the eHealth module of this study (consumption of vegetables, fruit, sugary beverages, and unhealthy snacks) are briefly assessed using 2 items per behavior taken from an existing questionnaire [41]. For example: "How many days in the past week did you eat fruit?" and "How many pieces of fruit on average did you eat per day?"

Determinants of Dietary Habits and Physical Activity

Attitude, Social Influences, and Self-Efficacy are measured for the 5 behaviors targeted in the eHealth module (physical activity, consumption of vegetables, fruit, sugary beverages, and unhealthy snacks). For example: Attitude: "Eating 3-4 serving spoons of vegetables a day would be (1 "very unpleasant" – 7 "very pleasant") for me"; Self-Efficacy: "I am confident I would be able to eat at least 2 pieces of fruit each day, if I wanted to" 1 "very untrue" – 7 "very true" [20].

Demographics

The questionnaire package started with a short demographic background (age, school, country of birth child and parents, gender, dominant hand [as a control variable for the EF battery response button box]). Further demographic details were collected from the parents (Socioeconomic Status—a correlate of EF [42], medication).

To ensure maximal participation, both the EF test battery and the Web-based questionnaire were administered at school. Moreover, 30 identical laptops and response button boxes were used to ensure maximum accuracy in measuring reaction times. Administration of the task battery and questionnaires took place on different days, to minimize load and maximize children's motivation to keep performing well. Everyone was measured within a span of 5 weeks, right before the start of the intervention and immediately after it ended. Trained research assistants (graduated psychology masters) were present at all times to supervise and instruct in the classrooms, as well as help slow readers work their way through the survey, when needed (this only happened a few times). All questionnaires had been normed for our age group, indicating readability should be decent. The task battery was administered in small groups of 5, the questionnaire in the entire group at once. While completing the computer task battery in small groups, children wore special noise-canceling headphones to avoid distraction. Furthermore, scores below chance levels (which indicates random responses) will be removed from the dataset. The strain on children was not small by any standards, but satisfactory pilot-testing and similar experiences in the field by supervising professors on the project team gave us confidence that the setup of measuring would run smoothly—which it did. The measurements concluded with a brief assessment of weight and height (body mass index, BMI). These anthropometrics were measured using standard procedures [43]. Both height (using the SECA 213 stadiometer) and weight (using the SECA 877 scales) were

assessed without shoes or heavy clothing to the nearest 1 mm and 0.1 kg, respectively. BMI was calculated as weight/height squared (kg/m^2) and Z-scores from age- and sex-specific reference values. Academic performance will also be taken into account during analysis using standardized national test scores (ie, CITO, the most widely used test in the Netherlands, designed by Centraal Instituut voor Toetsontwikkeling).

Teachers

Teachers are a valuable source of information regarding the children but were not included in the measurements because their time is very limited and scoring an entire class group is time-consuming. However, during the program implementation, close contact between teachers and the development team was maintained, to gain insight in the workings and feasibility of the intervention materials. Continuous feedback was encouraged and welcomed, to further improve and fine-tune the games and activities. After the intervention had taken place, an extensive (process) evaluation followed, including an assessment of fidelity and completeness.

Parents

We did include parents, for whom we composed a Web-based questionnaire pertaining questions about their child's behavior. This was mainly because self-report questionnaires given to 9- to 11-year-old children could not provide an accurate overview. Note: we will only describe the BRIEF-parent scale in the following overview, as the rest of the measurements are similar to those administered directly to the children, but then from the parent *about* their child.

The Web-based questionnaire for parents included:

- Strengths and Difficulties Questionnaire
- Behavior Rating Inventory of Executive Function (BRIEF-parent). The BRIEF is an 86-item rating scale developed to assess, via parent and teacher reports, manifestations of executive function in the everyday lives of children aged 5-18 years [44]. The BRIEF yields an overall Global Executive Composite score composed of 2 indexes called the Behavioral Regulation Index (child's ability to Inhibit [impulses], Shift [between tasks], and Emotional Control) and the Metacognition Index (child's ability to Initiate [start a task], Working Memory, Plan/Organize, Monitor [their own behavior], and Organization of Materials)
- Attention-Related Cognitive Errors Scale (ARCES)
- Child's physical activity and dietary habits
- Demographics (including socioeconomic status)

Statistical Analyses

As it was not feasible to estimate population means or SDs with our new computer task battery (designed to measure our main outcome, EF's), and we aimed to include as many schools as was practically possible, a power analysis for this study is not included. Unfortunately, we were not able to reach the recommended critical sample size of 50 at the group level [45]. Statistical techniques to compensate for this potential lack of

power for certain multilevel analyses will be considered and investigated carefully. We will assess the effectiveness of the TyM program using multilevel analyses (3 levels: student [$n=800$], class [$n=34$], and school [$n=13$]), to adjust for clustering of observations within a class or school. Randomization took place at the school level. The potential mediation our primary outcome, EF, exerts on our secondary outcomes (healthy behaviors: physical activity and healthy eating) will be investigated using the Baron and Kenny's method [46], adding EFs as a covariate. Note that the intervention and measurements have been concluded, but the data have not yet been completely analyzed.

Results

Results are expected to be submitted for publication in 2018.

Discussion

This study design protocol describes the cluster randomized trial to test the effectiveness of TyM, an intervention designed to enhance EFs among elementary school children aged between 9 and 11 years. Multiple modules (focused physical activity, cognitive games, and socioemotional development) are combined in TyM to increase the chances of EFs to improve and broad transfer to occur (translation of cognitive effects into daily life improvements, such as physical activity, adaptive emotion regulation, and healthy eating). Although broad transfer has not yet been demonstrated in the field, leading experts suspect combining approaches may yield promising results [2,10-12]. TyM is novel in the sense that it combines a physical-, cognitive-, and socioemotional approach in one integrated program. The development of the intervention and why EFs are of such cardinal importance to a healthy and happy life are described in a separate paper (J Bervoets et al, unpublished data, 2018). EFs are the very core of the entire project, which is why careful attention was paid to the measurement of these. An extensive 1 hour computer task battery was designed, with 2 tasks per sub-EF; impulse control: Flanker and Go/No-Go; working memory: N-Back and Running Span; cognitive flexibility: Attention Switching Task and Dots/Triangles. Additionally, questionnaires measured attention, concentration, emotion-regulation, social/behavioral problems, physical activity, and healthy eating. BMI was also measured. The TyM data will be enriched with academic performance and socioeconomic status from a provincial database to investigate the relations between our variables of interest. We hope to shed more light on the intricate connections between EFs, healthy behaviors, academic performance, and emotion regulation. Considering the vast array of possible positive outcomes of training EFs, efforts in this direction are warranted and justified. Given the intense nature of optimal cognitive training, and significant personal differences, combining various approaches in a playful context seemed like something teachers and pupils could continue doing wholeheartedly for a longer period of time.

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Authors' Contributions

JB, LMJ, GK, SM, and HdV conceived the study and developed the materials. JB, LMJ, and GK drafted the manuscript. All authors provided feedback on the manuscript, and read and approved the final text.

Conflicts of Interest

HdV is the scientific director of Vision2Health, a collaborating company between Maastricht University and OverNite Software Europe with the aim of offering proven effective methods in the field of health education. JB, LJ, SM, and GK declare that they have no conflicts of interest.

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Abbreviations

ARCES: Attention-Related Cognitive Errors Scale

AST: Attention Switching Task

BMI: body mass index

BRIEF: Behavior Rating Inventory of Executive Function

CITO: Centraal Instituut voor Toetsontwikkeling (Central Institute for the Development of Tests)

EF: executive function

FEEL-KJ: Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (Questionnaire for the Assessment of Emotion Regulation among Children and Adolescents)

ISI: interstimulus interval

PAQ-C: Physical Activity Questionnaire for Children

SDQ: Strengths and Difficulties Questionnaire

SRI: stimulus and response incongruent

TyM: Train your Mind

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Protocol

Individually Tailored, Adaptive Intervention to Manage Gestational Weight Gain: Protocol for a Randomized Controlled Trial in Women With Overweight and Obesity

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Abstract

Background: High gestational weight gain is a major public health concern as it independently predicts adverse maternal and infant outcomes. Past interventions have had only limited success in effectively managing pregnancy weight gain, especially among women with overweight and obesity. Well-designed interventions are needed that take an individualized approach and target unique barriers to promote healthy weight gain.

Objective: The primary aim of the study is to describe the study protocol for Healthy Mom Zone, an individually tailored, adaptive intervention for managing weight in pregnant women with overweight and obesity.

Methods: The Healthy Mom Zone Intervention, based on theories of planned behavior and self-regulation and a model of energy balance, includes components (eg, education, self-monitoring, physical activity/healthy eating behaviors) that are adapted over the intervention (ie, increase in intensity) to better regulate weight gain. Decision rules inform when to adapt the intervention. In this randomized controlled trial, women are randomized to the intervention or standard care control group. The intervention is delivered from approximately 8-36 weeks gestation and includes step-ups in dosages (ie, Step-up 1 = education + physical activity + healthy eating active learning [cooking/recipes]; Step-up 2 = Step-up 1 + portion size, physical activity; Step-up 3 = Step-up 1 + 2 + grocery store feedback, physical activity); 5 maximum adaptations. Study measures are obtained at pre- and postintervention as well as daily (eg, weight), weekly (eg, energy intake/expenditure), and monthly (eg, psychological) over the study period. Analyses will include linear mixed-effects models, generalized estimating equations, and dynamical modeling to understand between-group and within-individual effects of the intervention on weight gain.

Results: Recruitment of 31 pregnant women with overweight and obesity has occurred from January 2016 through July 2017. Baseline data have been collected for all participants. To date, 24 participants have completed the intervention and postintervention follow-up assessments, 3 are currently in progress, 1 dropped out, and 3 women had early miscarriages and are no longer active in the study. Of the 24 participants, 13 women have completed the intervention to date, of which 1 (8%, 1/13) received only the baseline intervention, 3 (23%, 3/13) received baseline + step-up 1, 6 (46%, 6/13) received baseline + step-up 1 + step-up 2, and 3 (23%, 3/13) received baseline + step-up 1 + step-up 2 + step-up 3. Data analysis is still ongoing through spring 2018.

Conclusions: This is one of the first intervention studies to use an individually tailored, adaptive design to manage weight gain in pregnancy. Results from this study will be useful in designing a larger randomized trial to examine efficacy of this intervention and developing strategies for clinical application.

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KEYWORDS

adaptive intervention; randomized controlled trial; mHealth; intervention study; overweight; obesity; pregnant women; exercise; nutrition science; gestational weight gain; body weight maintenance

Introduction

Background

Maternal weight gain in pregnancy is necessary for healthy fetal development [1]. The Institute of Medicine [1] recommends that appropriate weight gain for normal weight women is 25-35 pounds, whereas weight gain for overweight (15-25 pounds) and obese (11-20 pounds) women is less; any weight above these upper guidelines is considered excessive or high. High gestational weight gain (GWG) is strongly related to and independently predicts adverse pregnancy outcomes (eg, preterm delivery, gestational diabetes, and pre-eclampsia), greater adiposity, postpartum weight retention, and long-term obesity and cardiovascular disease [1,2]. Maternal obesity and high GWG also elevate infant risks such as macrosomia and early onset of obesity and diabetes [1]. As GWG is a modifiable factor that can be targeted to reduce adverse risks, managing GWG is critical for the mother, and can influence the etiology of obesity for offspring at a crucial time in the life cycle. However, over 50% of women enter pregnancy as already overweight (body mass index, BMI, 25-29.9 kg/m²) or obese (BMI ≥30 kg/m²) [3], and nearly 60% of women with overweight/obesity gain more weight in pregnancy than that recommended by the Institute of Medicine [1], which suggests they have particular challenges with managing their weight.

Past randomized intervention trials have shown that behavioral interventions can effectively manage weight in pregnant women [4-7] when they “mirror” effective programs in nonpregnant women such as using calorie goals, frequent contact and weight and dietary intake monitoring, and promoting healthy eating and exercise behaviors [8-10]. However, the effectiveness of these interventions has mainly been demonstrated in normal weight women. The results of studies including women with overweight and obesity are mixed. Several studies found little to no effect on GWG [5,6,11-13], whereas other interventions observed some effects [14,15] but were based on older guidelines [16] that were less restrictive than the current guidelines [1]. One study using current guidelines found a significant reduction in GWG (23 pounds) among women with obesity participating in a lifestyle intervention group compared

with the 30 pound gain in the control group [17]. Both groups, however, exceeded the Institute of Medicine GWG guidelines [1]. In short, women with overweight and obesity have unique challenges with managing weight that may likely require a more intensive and tailored approach than what is traditionally delivered in usual prenatal care or has been tested in past interventions.

One strategy that has been used to facilitate behavior change in other areas (eg, mental health issues, child behaviors, weight loss) [18-20] is an adaptive intervention (also known as a dynamic treatment regime or adaptive treatment strategy) [21,22]. In an adaptive intervention, a sequence of intervention strategies or dosages is tailored to an individual’s needs (similar to clinical practice) as opposed to a “one size fits all” intervention approach [23]. Adaptive interventions include critical decision points (eg, which intervention to start with, when and how to measure signs of response or nonresponse), intervention components (eg, set of intervention options at each critical decision point), tailoring variables (eg, variables expected to impact the effect of the component), and decision rules (eg, links tailoring variables to the intervention components) [24]. Moreover, principles of control systems engineering can be applied to an intervention context by using decision algorithms (controllers) to regulate a dynamical system to optimize intervention outcomes [25]. For example, control systems engineering can be used to construct and estimate a dynamical model that considers how changes in an outcome (eg, weight) are related to planned and self-regulatory behaviors (eg, dietary intake, physical activity) over time. An intervention that helps each pregnant woman with overweight and obesity to control GWG on a weekly basis and adapts to her unique needs over the course of pregnancy may be a promising strategy for managing weight in pregnancy. However, we are not aware of prior research that has used this intervention approach to manage weight gain in pregnancy.

Objectives

The primary aim of this publication is to describe the study protocol for Healthy Mom Zone, an individually tailored, adaptive intervention for managing weight in pregnant women with overweight and obesity. We will explain the conceptual

framework, theoretical components, intervention dosages, and decision rules for how and when to adapt the intervention. We then describe the intensive longitudinal data collection procedures and the methods for conducting poststudy participant interviews to examine program compliance, dosage exposure, and participant responsiveness. We will also explain the plan to establish initial validation of the intervention by examining impacts of the program on GWG (ie, average weekly GWG of intervention vs control group; meeting individual GWG goals based on prepregnancy weight status), energy intake, physical activity, planned self-regulatory behaviors, and related maternal health outcomes. This work aims to use principles of control systems engineering to optimize the intervention for future application; in other words, to inform how the intervention can effectively and efficiently manage GWG in pregnant women with overweight and obesity.

Methods

Ethics Approval and Consent to Participate

This study has been approved by the Pennsylvania State University Institutional Review Board (Study #00000122) and Clinical Research Center (#319). All legal and data protection issues are discussed with the responsible authorities, and all participants are required to provide active informed consent.

Overview of Healthy Mom Zone Study Design

The intervention is currently being tested in a longitudinal study design among a cohort of pregnant women with overweight and obesity randomized to either the intervention or control group from approximately 8-36 weeks gestation. [Figure 1](#) summarizes the flow of participants through the study using the Consolidated Standards of Reporting Trials template [26]. Study measures

are obtained at baseline, throughout the course of the intervention (eg, daily, weekly, and monthly), and at follow up (see [Table 1](#)). GWG is evaluated weekly and decision rules are used in 3-4 week cycles to decide when and how the intervention may be adapted for an individual. The decision to evaluate GWG in 3-4 week cycles was based on the following: (1) clinical insight and judgment (eg, prenatal care visits for most women occur in 3-4 week cycles, so we used the same cycle for our GWG evaluations), (2) reducing participant burden (eg, the 3-4 week cycle allowed women to adjust to the dosages before adaptations are made), and (3) being proactive about adjusting the intervention dosage in real-time before a woman's weight exceeds her goal. In addition, mHealth tools are used to allow participants to self-monitor behaviors (ie, weight, physical activity, dietary intake). The study staff can review the data collected from the monitors and provide the participants with real-time feedback to facilitate compliance (eg, contact participants when the devices are not working or not being used according to the study protocol). All participants are compensated for their time spent on completing the study measures (receive gift cards and cash for pre- and postmeasures); women participating in the intervention do not have to return their Wi-Fi weight and food scales. We will use the data collected in this study and dynamical modeling from control systems engineering (system identification) to express progression of GWG over time. We will identify a customized intervention plan for each woman based on her energy intake, physical activity, planned and self-regulatory behaviors, and the extent to which she is meeting GWG goals over pregnancy. This will lead to final intervention modifications and result in an individually tailored, adaptive and optimized intervention, of which we will test efficacy in a future randomized controlled trial.

Figure 1. Flow of participants through Healthy Mom Zone Intervention (still underway) as per Consolidated Standards for Reporting Trials guidelines. Participants allocated to intervention group could be assigned to various step-ups throughout the intervention time period. Step-ups will vary by individual and time-point of intervention and gestation. Incomplete cells are due to ongoing data collection.

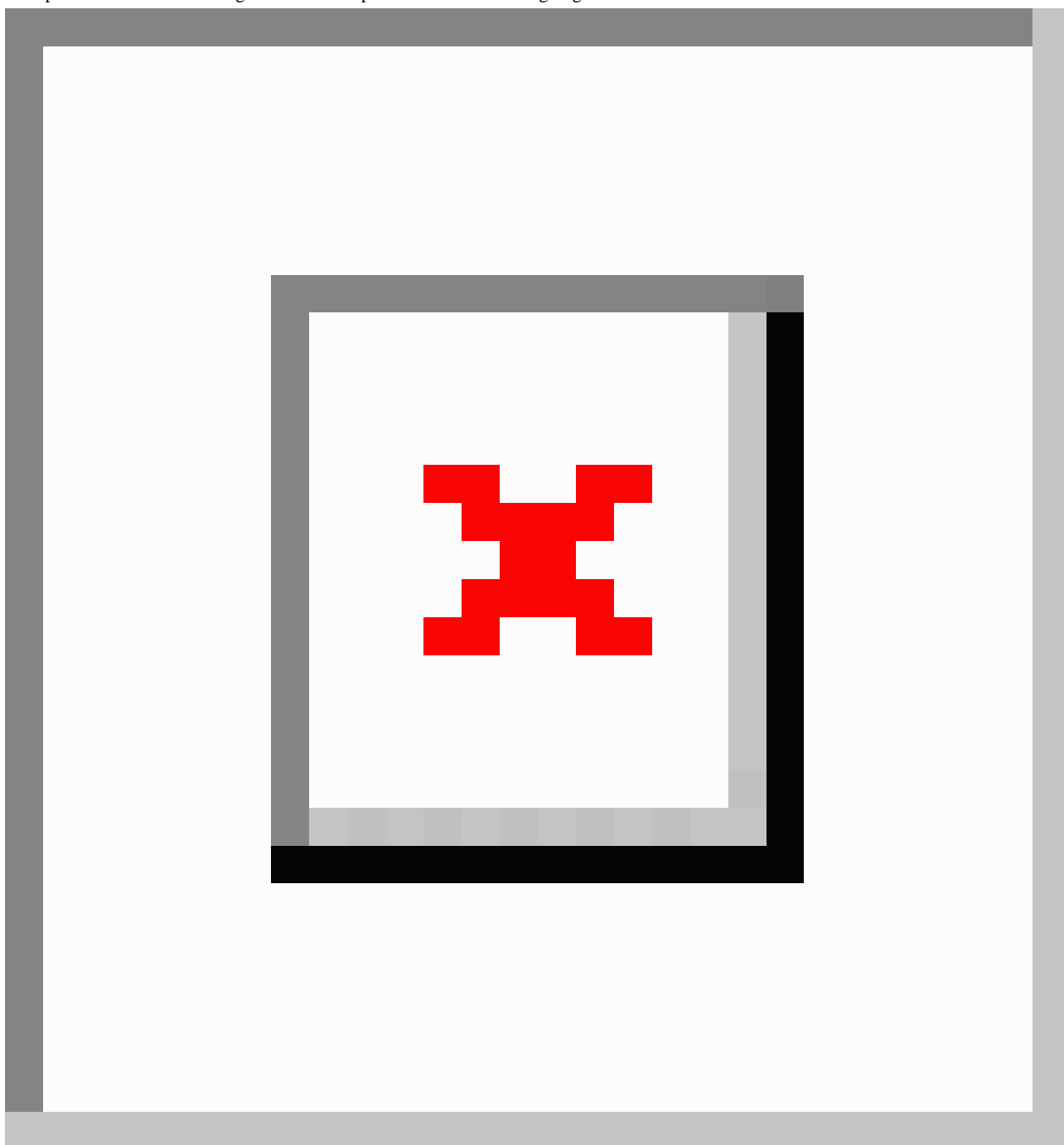


Table 1. Healthy Mom Zone measurement protocol. X designates when the measurement had taken place. All participants completed this measurement protocol.

Variable	Assessment	Time point							
		Pr ^a	Po ^b	D ^c	W ^d	BiW ^e	M ^f	Pp ^g	
Weight and weight gain	High Precision Stand-On Adult Scale	X	X						X
	FitBit Aria Wi-Fi Smart Scale			X					X
Height	Stadiometer	X							
Serum blood	Macronutrients	X	X						
Adiposity	Air-Displacement Plethysmography (BODPOD) Body Composition	X	X						X
Healthy eating behaviors	MyFitnessPal Phone App				X				
	3-Factor Eating Questionnaire	X	X					X	
	Remote food photography		X						X
Physical activity behaviors	Actigraph (time spend in moderate-intensity activity)	X	X					X	
	Jawbone Wrist-Worn Activity Monitor	X	X	X					X
	Physical activity log (mode and min activity)								X
	Leisure-Time Exercise Questionnaire	X	X					X	
Weight attitude	Palmer attitudes toward weight in pregnancy	X	X					X	
Healthy eating and exercise motivational determinants	Attitude, subjective norm, perceived control, intention	X	X					X	
	Healthy eating and exercise beliefs	X	X		X				
Self-regulation	Self-regulation index	X	X				X		
	Self-Regulation Questionnaire (self-regulatory function)	X	X				X		
	Self-control scale	X	X					X	
Sociodemographic	Health history Questionnaire	X							
	Pregnancy complications	X			X				
Self-efficacy	Sui Healthy Eating and Physical Activity Self-Efficacy Scales	X	X					X	
	Clark Weight Efficacy Scale	X	X					X	
Sleep behaviors	Pittsburgh Sleep Quality Index	X	X					X	
	Jawbone Wrist-Worn Activity Monitor	X	X	X					X
Psychosocial	Center for Epidemiological Studies Depression Scale	X	X					X	
	State Trait Anxiety Inventory	X	X				X	X	
	Body Areas Satisfaction Scale	X	X					X	
	Perceived Stress Scale	X	X		X				
	Pregnancy Figure Rating Scale	X	X					X	
	Rothbart Adult Temperament Scale	X							
Stress	Urine cortisol collection	X	X		X				X
Metabolism	Breezing device	X	X		X				X
Fetal Growth	Standard fetal ultrasound scans							X	

^aPr: preintervention.^bPo: postintervention.^cD: daily.^dW: weekly.^eBiW: biweekly.^fM: monthly.^gPp: postpartum.

Participants and Sample Size

The target sample for this intervention is 30 pregnant women with overweight and obesity (BMI range 25-45 kg/m²; >40 kg/m² with physician consultation); singleton pregnancy >8 weeks gestation; English-speaking; residing in or near Centre County, Pennsylvania; and with physician consent to participate. On the basis of our past research [27,28], this group comprises >85% of live births in Central Pennsylvania. Exclusion criteria are multiple gestation, diabetes at study entry, not overweight or obese, severe allergies or dietary restrictions, contraindications to prenatal physical activity [29], and not residing in area for duration of the study. The primary outcome of our study is GWG. Julious [30] effectively argues a sample size of 12 per group is adequate to assess feasibility and obtain sufficient precision of the mean and variance to perform a formal sample size and power calculation for a future larger randomized control trial with GWG as the primary outcome. With 24 participants (12 per group), we will have 80% statistical power to detect a standardized effect size (difference between 2 group means divided by SD) for GWG of 1.2 using a 2-sided test with significance level of $P=.05$. Factoring in participant dropout (conservative estimate of 25% based on our pilot work [31,32] and past research [5]), we will recruit 30 participants (15 intervention, 15 control).

Recruitment, Assignment, and Allocation

Women are recruited using on-site clinic, community-based, and Web-based strategies. At the clinic, nurses identify potential eligible women and refer them to a study staff member who is ready in the waiting room to speak with them about the study and, if interested, screen them for eligibility. Community-based recruitment includes hanging study flyers at local businesses, churches, campus, and community centers. Web-based recruitment occurs through the study website [33] and Facebook ads. Interested women call a toll-free number. A project staff member explains the study, obtains verbal assent to ask questions, and determines eligibility based on the inclusion criteria described above. Pregnant women with overweight and obesity are recruited between 8 and 12 weeks gestation and randomized to the intervention or control condition until about

36 weeks gestation. The study biostatisticians developed a randomization scheme using variable size, random permuted blocks to ensure the number of participants in each group is balanced after each set of B randomized participants, where B is the block size. Randomization to intervention ($n=15$) or control ($n=15$) groups uses 1:1 allocation; participants are entered consecutively. When a woman is eligible and informed consent is signed, a staff member requests randomization by a unique participant identification number.

Conceptual Framework

We used principles from the Theory of Planned Behavior [34] and self-regulation [35] for the conceptual framework of the Healthy Mom Zone Intervention (Figure 2).

The Theory of Planned Behavior assumes a person is motivated for a behavior (eg, managing GWG) when she has a positive attitude, believes that significant others want her to do the behavior (subjective norm), and has the perceived ability to do the behavior (perceived behavioral control) [34]. Self-regulation assumes that behavior is goal-directed and regulated by feedback control processes [35]. The participant engages in activities in which she can succeed, and this confidence in performance success can influence her perceived behavioral control. Thus, self-monitoring is a core strategy of behavior modification and a key aspect of the dynamical systems model to manage GWG in this study. The overall simulation model for GWG is depicted in Figure 3 and includes the following: (1) a 2-compartment energy balance model predicting changes in body mass as a result of energy intake and physical activity, (2) 2 Theory of Planned Behavior models describing how energy intake and physical activity are affected by behavioral variables, (3) a program delivery module relating magnitude and duration of components to inflows of the Theory of Planned Behavior models, and (4) 2 self-regulation units modeling how success expectancies in the intervention influence one's goal achievement motivation [36,37]. This model serves a vital role in evaluating the decision rules in the individually tailored intervention and in applying advanced strategies to produce decision frameworks for making program adaptations.

Figure 2. Conceptual framework for Healthy Mom Zone Intervention. HE: healthy eating; PA: physical activity, GWG: gestational weight gain.

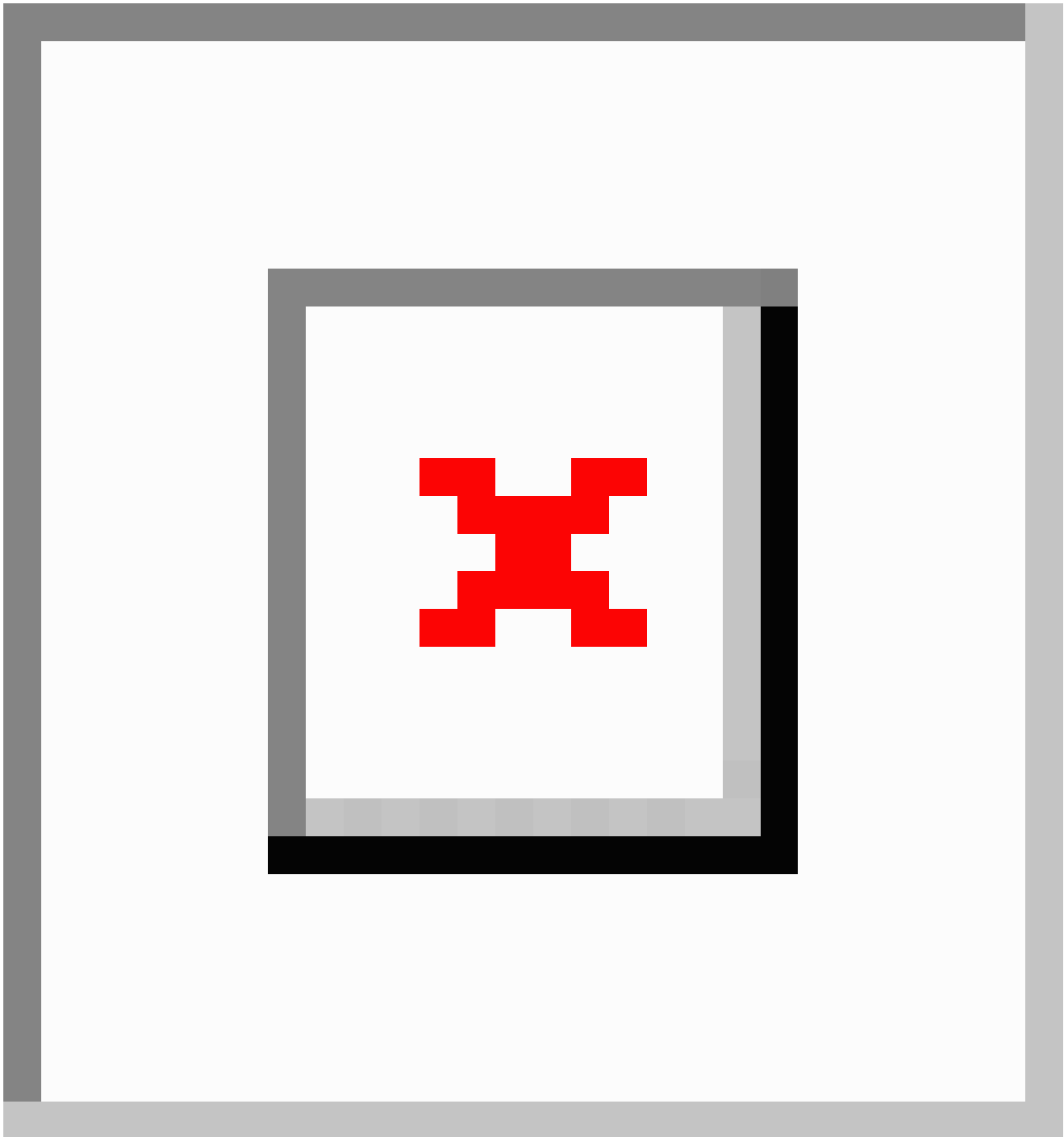
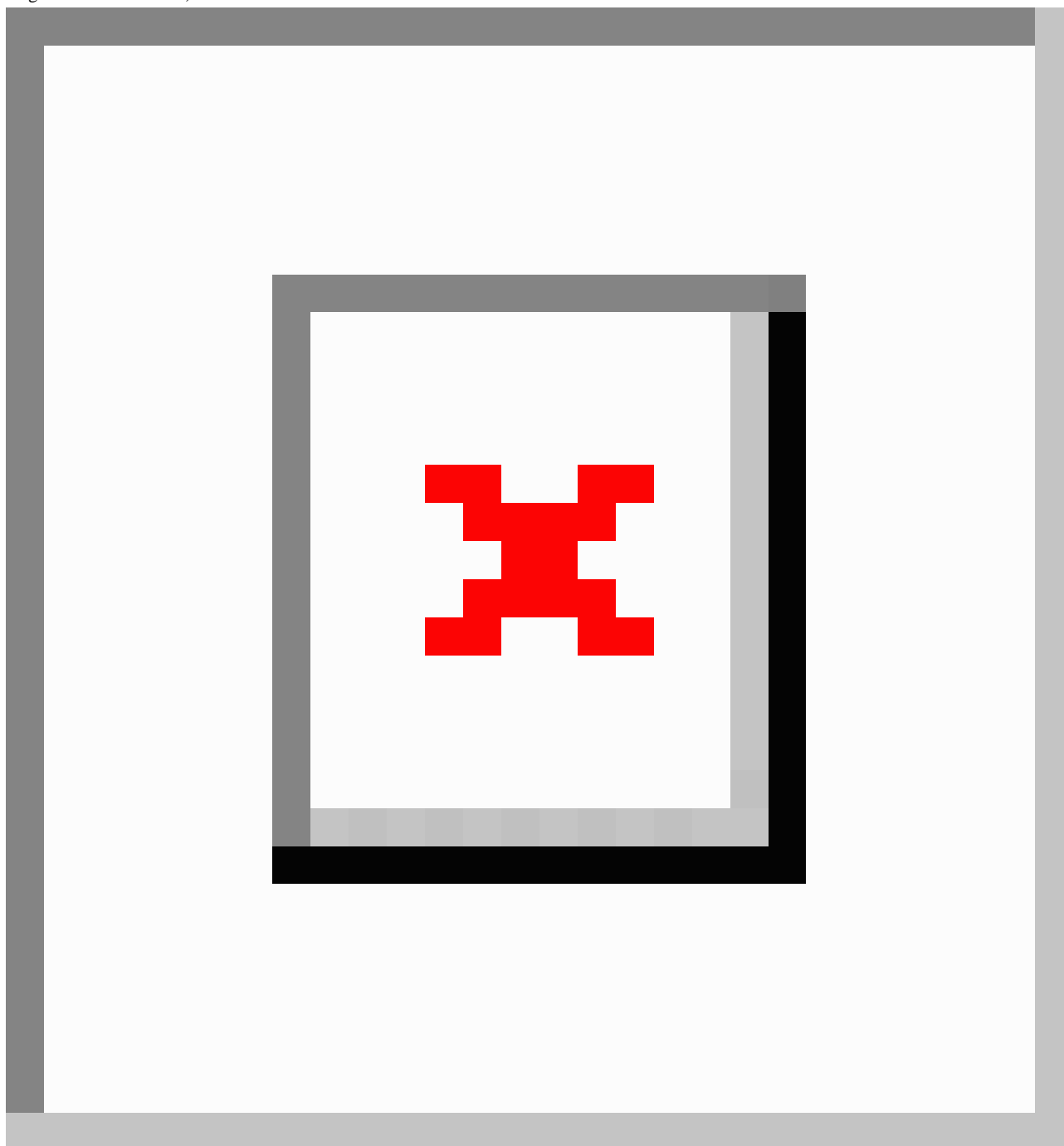


Figure 3. Energy balance model underlying the Healthy Mom Zone Intervention. TPB: Theory of Planned Behavior; $I_1 \dots I_n$: Intervention components; i : exogenous variables that serve as inputs for behavioral models; y_i : system outputs; ξ_1 : Behavioral belief \times evaluation of outcome; ξ_2 : Normative belief \times motivation to comply; ξ_3 : Control belief \times power of control belief; I_1 : Healthy Eating Education; I_2 : Healthy Eating Weekly Plan; I_3 : Healthy Eating Active Learning; I_4 : Goal Setting; I_5 : Physical Activity Education; I_6 : Physical Activity Weekly Plan; I_7 : Physical Activity Session; I_8 : Daily Weight Scale; I_9 : Dietary Record; I_{10} : PA monitor output. Black solid line shows input/output signals between models; Black dashed line shows self-regulation feedback loop; Blue dashed line shows intervention dosages which indicate how and when the intervention is adapted; Green dashed line shows tailoring variables that inform whether the intervention is adapted; Circle dashed line shows regular measurement of important outcomes (self-regulation intervention).



Healthy Mom Zone Intervention Components

The intervention components (see Figure 4) are informed by past research and our own pilot data [5-10,31,32,38,39]. Evidence from model lifestyle interventions [8-10,38], GWG interventions [5-7], and our research on promoting healthy behaviors [39-41] shows education, goal-setting and action planning, and self-monitoring can effectively manage weight.

Our past studies have shown that when people are taught how to set appropriate plans and goals, self-monitor, and manage their time, they are more likely to achieve their goals and see positive behavioral outcomes (eg, engage in healthy eating and exercise to manage weight) [39,42-44]. Furthermore, convincing evidence from past research [39,44,45-49] shows that healthy eating and physical activity active learning (eg, active participation in strategies to reduce energy density such as food

preparation and planning, portion size control, increasing intake of fruits and vegetables, meeting physical activity goals, and engaging in guided exercise sessions) are effective for lowering energy intake and managing body weight. We also learned from our pilot study [50] that women wanted to know more about how the target intervention behaviors (eg, weight, physical activity, dietary intake) were related to their baby’s growth, so we developed brief modules to inform women about the following: (1) current research studies (Featured Evidence and Baby’s Health) and (2) unique aspects of their baby’s growth (Baby Fun Facts); content is delivered weekly in this study via email.

Standard of Care Control Condition

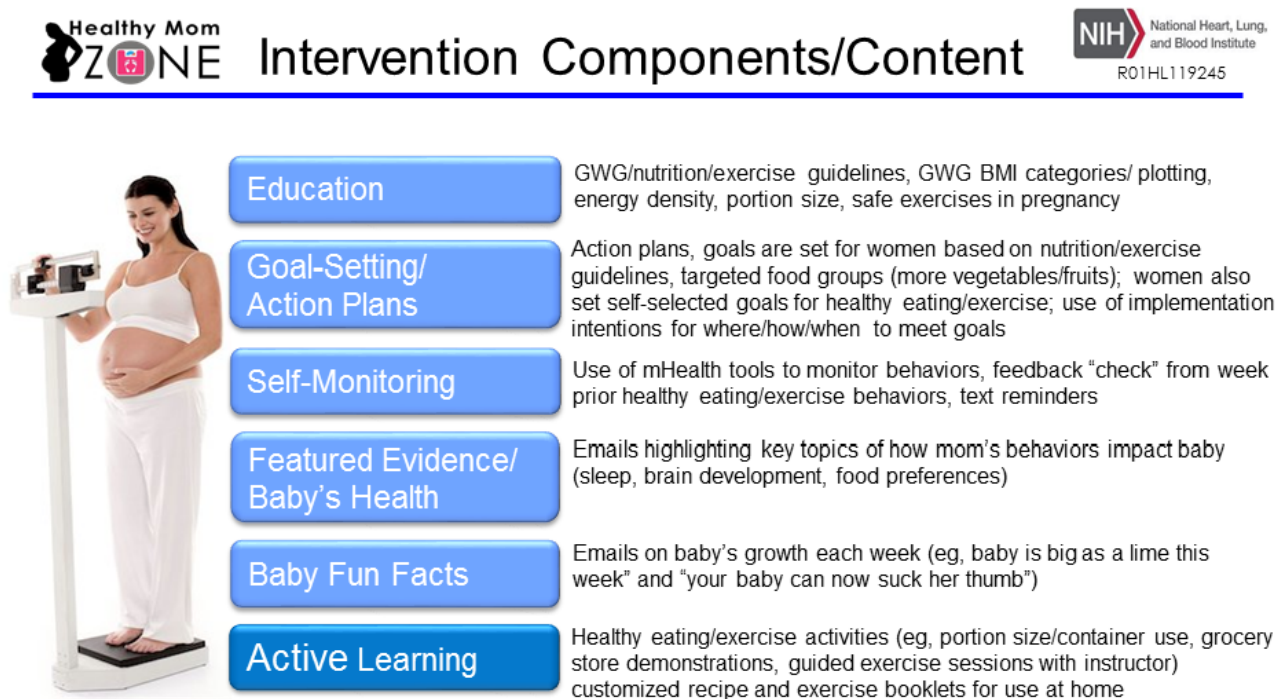
All women in the study receive standard prenatal care (eg, regular visits and prenatal counseling with health care provider; provider is not informed by the research team of randomization assignment). The women randomly assigned to the control condition also complete the same measurement protocol as the

intervention participants, which includes daily, weekly, and monthly assessments (see Table 1).

Healthy Mom Zone Intervention Description

Women randomized to the intervention group receive the baseline dosage, which includes for all women the intervention components (described above) of education, goal-setting and action plans, featured evidence on baby’s health, baby fun facts, and self-monitoring. Participants meet weekly with a study dietitian and are given customized calorie goals and a booklet developed for this study that contain customized healthy eating plans, recipes, and tailored meals to meet calorie goals. They are also given a physical activity booklet with customized and safe pregnancy-related exercises (see Multimedia Appendix 1). A study staff member reviews each woman’s weight, physical activity, and dietary intake via real-time data collection procedures and generates a report for the study dietitian to review with the participant at the next intervention session.

Figure 4. Healthy Mom Zone Intervention components. Components in light blue are in baseline intervention and delivered throughout the duration of the intervention. Active Learning component is adapted depending on decision rules and gestational weight gain (GWG) evaluations. BMI: body mass index.



The dietitian plots weekly GWG using individualized charts that illustrate GWG within the context of the Institute of Medicine guidelines and discusses strategies to overcome barriers to managing weight and engaging in healthy eating and physical activity behaviors. Women in the intervention also complete a 15-min postintervention exit interview at their post assessment to provide their feedback and perspective on multiple aspects of their intervention experience (eg, likes and dislikes about using the mHealth tools, adaptive dosages, active learning activities, completing study measures). Intervention sessions are randomly audio-recorded and coded for fidelity.

Study Setting and Procedures

All participants, regardless of intervention assignment, complete the same study measurement protocol. The study setting includes onsite visits at the Penn State Clinical Research Center (University Park campus) and at-home participation. Interested and eligible women complete a preintervention assessment at the Penn State Clinical Research Center after the study is described and written consent is obtained. A study clinician assesses height, weight, blood pressure, and conducts a physical exam to identify health symptoms that may preclude study participation [29]. Women complete self-reported measures of their healthy eating/physical activity behaviors, knowledge, planned and self-regulatory behaviors, motivational determinants, demographics, and dietary intake using onsite

paper and pencil and Web-based data capture software (Research Electronic Data Capture) [51].

Women then complete an air displacement plethysmography body composition assessment following a standardized protocol that takes approximately 30 min. Participants complete these same measures again at the postassessment at approximately 36 weeks gestation. In addition, during the course of the study all women are given a Wi-Fi scale for wireless uploading of daily weight, food scale to monitor daily intake, and log to record food and beverages (and amounts) consumed, and 2 monitors (wrist-worn activity monitor worn daily; waist-worn accelerometer worn in 2-week cycles) to track physical activity. Participants are asked to use these mHealth devices continuously over the course of the entire study. Women track dietary intake on 2 weekdays and 1 weekend using a mobile phone app. Measures are obtained at baseline, during the intervention (daily, weekly, and monthly), and postintervention. All participants are compensated up to US \$420 in check or gift card for the pre and post, weekly, and monthly assessments over the study period. In addition, the intervention participants get to keep their Wi-Fi weight and food scales at the end of the study (control participants return them), and they receive a US \$20 check if they attend 90% (25/28) or more of the intervention sessions.

Decision Rules and Adapting the Intervention Dosage

A set of decision rules were developed to evaluate GWG that are based on the Institute of Medicine GWG guidelines (ie, overweight=15-25 pounds; obese=11-20 pounds) [1], our own research [36,37,50], and clinical insight that inform when and how to adapt the components. A computerized applet is used to plot women's weight against individual weight gain trajectories with lower and upper bounds for the GWG guidelines [52,53]; GWG is evaluated weekly and the values are compared with average weekly weight ranges for overweight (eg, 0.5-0.7 pounds) and obese (eg, 0.4-0.6 pounds) women [1]; these weekly weights are then evaluated in 3-4 week cycles to determine if and when the intervention dosage should be adapted (see Multimedia Appendix 2). The rationale for adapting the dosages is based on each woman's self-regulatory abilities to manage GWG. For example, if the woman is within her GWG goal (ie, weekly weight gain ranges according to the Institute of Medicine guidelines) [1], she will continue to receive the same level of the intervention for the next cycle as she is adequately self-regulating her weight with the amount of intervention dosage that she's receiving. However, if she is exceeding her GWG goal, the intervention is adapted (ie, dosage is stepped up). That is, she continues to receive the baseline intervention, but then she receives additional active learning components (eg, step-up 1 with cooking and grocery store demonstrations; onsite exercise session led by an instructor) to help better self-regulate her weight. If she exceeds her GWG goal at the next evaluation cycle, the intervention will be adapted again (ie, baseline + step-up 1 + step-up 2) with other active learning components (eg, portion size and containers; second onsite exercise session with instructor) added to provide more intensive intervention assistance and supportive control to better manage GWG. This evaluation process continues over the course of her pregnancy until the end of the intervention (ie, around

36 weeks gestation) and/or a maximum of 5 possible dosage increases (see Multimedia Appendix 3). The sequencing of the adaptive dosages was determined during pilot testing by examining combinations of active learning strategies with good user acceptability, and we identified the maximum number of dosage increases that resulted in "too much intervention burden" and led to participant dropout (ie, more than 5 adaptations) [50]. If a participant is under her GWG goal [1] and/or any safety concerns emerge (eg, complication such as anemia, fetal issue), we consult with the study obstetrician who makes recommendations on if and/or how intervention dosage changes should be made.

Outcome Measures

The measurement protocol is presented above in Table 1. The primary outcome measure is GWG. Weight and GWG are assessed pre- and postintervention at the Penn State Clinical Research Center using standardized procedures (eg, measured in duplicate to nearest kilogram using a high-precision stand-on adult scale; wearing undergarments and gown) and daily at home using the Wi-Fi wireless scale. Secondary outcomes include adiposity (body composition), healthy eating behaviors, physical activity behaviors, knowledge, motivational determinants, self-regulation, psychological well-being, sleep, serum blood for macronutrients, stress (cortisol), metabolism, and fetal growth.

Data Collection

Data on the primary and secondary outcome variables above are collected in addition to participant sociodemographic characteristics (eg, age, BMI status) to understand the influence of potential moderators on the primary and secondary outcome variables. Standardized procedures were developed for data collection, recording of errors, and a comprehensive data quality assurance program to ensure complete, accurate, and valid data while limiting variability in data recording. Study data are managed using a secure Web app that provides user-friendly Web-based case reports, real-time data entry validation audit trails, and a deidentified data export mechanism to commonly used statistical packages.

Data Analysis

To establish initial validation of the intervention, contrasts constructed from linear mixed-effects models [54] will be used to assess differences between the intervention and control groups with respect to changes in continuous outcomes over time (from pre- to postintervention): changes in primary (GWG, energy intake, physical activity, planned/self-regulatory behaviors) and secondary outcomes (serum blood biomarkers, adiposity, knowledge). Linear mixed-effects models are an extension of ordinary regression models that account for within-subject variability inherent in longitudinal studies. Generalized estimating equations [55] with a logit link will be used to assess differences between the intervention and control groups with respect to dichotomous outcomes over time. If deemed necessary, confounding variables (eg, prepregnancy weight, age, obstetric complications) will be included as covariates. With respect to the participants meeting individual GWG goals based on prepregnancy BMI status [1], we will look at each

woman and determine whether she met her GWG goal. We will code participants as “0” for GWG within goal, +1 for GWG over goal, and -1 for GWG under goal. A chi-square test will be used to assess differences between the intervention and control groups on this 3-level ordinal variable (ie, -1,0,1) assessing individual GWG goals. All hypothesis tests will be 2-sided, and analyses will be performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) or R software (R Foundation for Statistical Computing, Vienna, Austria).

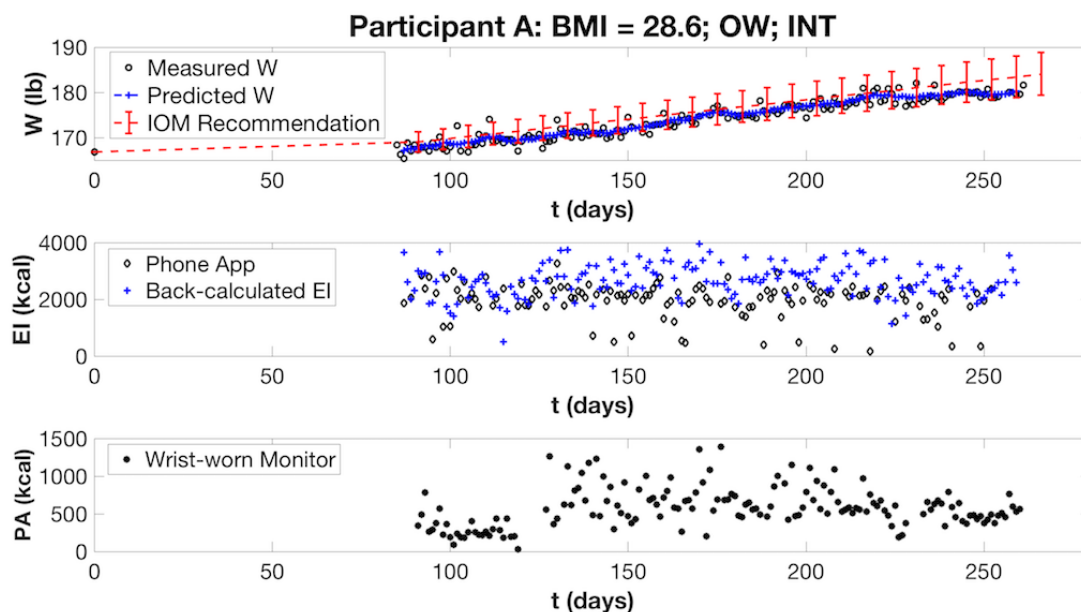
Modeling development and simulation are done in Matlab with SIMULINK (The MathWorks, Inc., Natick, MA). Functional data analysis modeling for time-varying modeling will rely on SAS. Weight predictions based on a first-principles energy balance model can be performed using measurements of a participant’s energy expenditure (physical activity and resting metabolic rate) and energy intake. Alternatively, energy intake can be estimated from the energy balance model using the measured weight gain and physical activity, which can then be compared with self-reported data [56,57]; this information can

be used by dietitians to provide informative health guidance. Intensive measurements of the Theory of Planned Behavior constructs are used to build participant-based dynamical models using semiphysical model identification techniques. The integration of these behavioral models with energy balance models can be used to evaluate and implement decision policies based on control systems engineering for an intensively adaptive intervention, specifically Hybrid Model Predictive Control [37,58].

Results

The targeted sample of pregnant women with overweight and obesity has been successfully recruited between January 13, 2016, and July 1, 2017. Baseline data have been collected for all participants. To date, 24 participants have completed the study and postintervention follow-up assessments, 3 are currently in progress, 1 dropped out, and 3 women had early miscarriages and are no longer active in the study.

Figure 5. Preliminary visualization of a Healthy Mom Zone Intervention participant’s gestational weight gain data. The intervention participant’s measured weight is plotted against her predicted weight (based on the computerized applet) and the Institute of Medicine upper and lower ranges for recommended weight gain for a woman who is OW. Her EI (measured with phone app and estimated with a back-calculation formula) and PA (measured with wrist-worn activity monitor) are also plotted. BMI: body mass index; OW: overweight; INT: intervention participant; W: weight; EI: energy intake; PA: physical activity; kcal: kilocalories.



Of the 24 participants, 13 women have completed the intervention to date, of which 1 (8%, 1/13) received only the baseline intervention, 3 (23%, 3/13) received baseline + step-up 1, 6 (46.1%, 6/13) received baseline + step-up 1 + step-up 2, and 3 (23%, 3/13) received baseline + step-up 1 + step-up 2 + step-up 3.

Preliminary results are presented in Figure 5 for 1 participant who is overweight and was randomized to the intervention group (from gestational age day 85 through day 261). As shown in Figure 5, her actual weight remained within that recommended by the Institute of Medicine [1], whereas under-reporting is observed in her self-reported energy intake compared with a back-calculation method based on our maternal energy balance

model ([56]; see reference for more detailed explanation of the back-calculation method). Using the back-calculated energy intake for weight prediction, the model-predicted weight follows closely to her measured weight. Data analysis is still ongoing through spring 2018.

Discussion

Principal Findings

To the best of our knowledge, this is the first study that is testing the feasibility of an individually tailored, adaptive intervention to manage GWG in pregnant women with overweight and obesity. This intervention, Healthy Mom Zone, aims to improve

upon past interventions by addressing gaps in the literature, specifically among pregnant women with overweight and obesity, by providing a more individually tailored and adaptive approach to effectively manage weight gain during pregnancy. Although this intervention was deliberately intensive to understand if this approach can effectively manage GWG, future plans for this line of research will explore how the Healthy Mom Zone Intervention can be further adapted to women's individual needs.

For example, we may learn from the study findings that some women can effectively manage their GWG with less intervention, and therefore, we can step down the intervention for them, whereas other women need the step up to keep their weight within their goals. This approach will also increase the clinical application and utility of the intervention.

Strengths and Limitations

There are several positive features of this study. This study has strong public health relevance and clinical significance for the future management of GWG. We have also incorporated several innovative aspects into the study, including the use of (1) novel decision rules to choose when and how to adapt the intervention, (2) mHealth tools for self-monitoring of behaviors and real-time data collection to provide feedback to the participants, and (3) a unique computerized applet to generate individualized weight gain trajectories for comparing actual weight to the Institute of Medicine guidelines. In addition, customized eating and physical activity plans developed for this study aid in reducing participant barriers to engaging in healthy behaviors during pregnancy. Moreover, the intensive longitudinal data collection protocol allows for a myriad of systems approaches in support of implementing and evaluating intensively adaptive interventions [25,56-58]. Intensive data collection enables the application of system identification and state estimation approaches from engineering that, in turn, build comprehensive dynamical models

for GWG used in adaptive intervention optimization. These methods can be used to estimate and correct energy intake over time, despite some missing data.

There are also some limitations of this research. The small sample size, although adequate for examination of the primary outcome (GWG), precludes the ability to make assumptions at a population level. Moreover, the target population is a homogenous sample of women from largely rural and suburban areas in Central Pennsylvania, thus limiting the extension of the study findings to more culturally diverse and urban populations of pregnant women with overweight and obesity. We do plan to understand the application of Healthy Mom Zone to a more diverse sample of pregnant women in the future, including those who are normal weight, more culturally diverse, and reside in varied communities across the United States.

Conclusions

The data and knowledge obtained from this innovative intervention will be valuable for informing future studies aiming to manage GWG in pregnancy. We aim to learn from the study findings how to further adapt the intervention (eg, step up or down) to meet women's needs and customize the intervention based on women's individual characteristics. For example, we may learn that certain individual characteristics (eg, higher perceived behavioral control, lower stress) help women to self-regulate their weight better, and therefore, we can expand the intervention to better target these factors at the start of a pregnancy. The insight gained from this study as well as independent developments in mHealth tools and their use in clinical practice (eg, links to electronic records and provider communication) will also help to disseminate this individually tailored, adaptive intervention to effectively manage GWG in clinical practice—so that all pregnant women can be targeted to ultimately improve maternal and infant health outcomes and impact the etiology of obesity at a critical time in the life cycle.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Study booklets with customized healthy eating and physical activity material.

[[PDF File \(Adobe PDF File\), 222KB - resprot_v7i6e150_app1.pdf](#)]

Multimedia Appendix 2

Illustration of the decision rule for GWG evaluation and adapting dosages.

[[PDF File \(Adobe PDF File\), 68KB - resprot_v7i6e150_app2.pdf](#)]

Multimedia Appendix 3

Illustration of Healthy Mom Zone Intervention adaptive intervention design.

[[PDF File \(Adobe PDF File\), 73KB - resprot_v7i6e150_app3.pdf](#)]

Multimedia Appendix 4

CONSORT-EHEALTH checklist (V 1.6.1).

[[PDF File \(Adobe PDF File\), 715KB - resprot_v7i6e150_app4.pdf](#)]

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Abbreviations

- BMI:** body mass index
- EI:** energy intake
- GWG:** gestational weight gain
- INT:** intervention participant
- kcal:** kilocalories
- PA:** physical activity
- TPB:** Theory of Planned Behavior

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Protocol

Development and Evaluation of an Ethical Guideline for Decisions to Limit Life-Prolonging Treatment in Advanced Cancer: Protocol for a Monocentric Mixed-Method Interventional Study

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Abstract

Background: Many patients with advanced cancer receive chemotherapy close to death and are referred too late to palliative or hospice care, and therefore die under therapy or in intensive care units. Oncologists still have difficulties in involving patients appropriately in decisions about limiting tumor-specific or life-prolonging treatment.

Objective: The aim of this Ethics Policy for Advanced Care Planning and Limiting Treatment Study is to develop an ethical guideline for end-of-life decisions and to evaluate the impact of this guideline on clinical practice regarding the following target goals: reduction of decisional conflicts, improvement of documentation transparency and traceability, reduction of distress of the caregiver team, and better knowledge and consideration of patients' preferences.

Methods: This is a protocol for a pre-post interventional study that analyzes the clinical practice on treatment limitation before and after the guideline implementation. An embedded researcher design with a mixed-method approach encompassing both qualitative and quantitative methods is used. The study consists of three stages: (1) the preinterventional phase, (2) the intervention (development and implementation of the guideline), and 3) the postinterventional phase (evaluation of the guideline's impact on clinical practice). We evaluate the process of decision-making related to limiting treatment from different perspectives of oncologists, nurses, and patients; comparing them to each other will allow us to develop the guideline based on the interests of all parties.

Results: The first preintervention data of the project have already been published, which detailed a qualitative study with oncologists and oncology nurses (n=29), where different approaches to initiation of end-of-life discussions were ethically weighted. A framework for oncologists was elaborated, and the study favored an anticipatory approach of preparing patients for forgoing therapy throughout the course of disease. Another preimplementational study of current decision-making practice (n=567 patients documented) demonstrated that decisions to limit treatment preceded the death of many cancer patients (62/76, 82% of deceased patients). However, such decisions were usually made in the last week of life, which was relatively late.

Conclusions: The intervention will be evaluated with respect to the following endpoints: better knowledge and consideration of patients' treatment wishes; reduction of decisional conflicts; improvement of documentation transparency and traceability; and reduction of the psychological and moral distress of a caregiver team.

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KEYWORDS

ethical guidelines; treatment limitation; advanced cancer

Introduction

Decision-making to limit a tumor-specific and life-prolonging treatment in patients with advanced cancer is one of the most difficult tasks in end-of-life care and is often accompanied by psychological and ethical challenges. Many patients with advanced cancer receive aggressive chemotherapy close to death and are referred to palliative or hospice care too late, and die under therapy or in the intensive care unit [1-3]. Thus, the number of patients receiving chemotherapy between two weeks and death has been constantly rising [4]. The literature suggests that discussions about patients' end-of-life preferences and treatment limitation should occur much earlier. Such discussions have been associated with better patient outcomes in terms of increasing patients' quality of life and reducing patients' anxiety, distress, and depression [3,5,6].

However, in a previous study we demonstrated that only 37 of 76 patients (47%) with incurable cancer had discussions about limiting treatment or got involved in decisions about limiting tumor-specific or life-prolonging treatment (eg, do-not-resuscitate orders) [7]. Oncologists still have difficulties in discussing treatment limitation with their patients and feel unsure about when and how to initiate such discussions [8,9]. Against this background, we initiated a monocentric interventional study aimed at developing an ethical guideline for end-of-life decision-making, with a goal to increase oncologists' awareness of patients' treatment preferences, to increase patients' involvement in decision-making, and to reduce psychological and moral distress within a caregiver team. According to many evaluational studies, guidelines can change clinical practice and may lead to the improvement of physician performance and patient outcomes [10,11].

While there are many studies on impact and uptake of guidelines in medical practice, ethical guidelines remain underrepresented in research and the impact of such guidelines in medical practice is not well studied. In the following protocol, we explain our study design for evaluating the impact of ethical guidelines on the practice of clinical decision-making regarding treatment limitation. The overall aims of this three-stage interventional Ethics Policy for Advanced Care Planning and Limiting Treatment (EPAL) Study are: (1) to develop an ethical guideline for end-of-life decision making, and (2) to evaluate its impact on decision-making practice. The guideline will be evaluated with regard to the following outcomes: better knowledge and consideration of patients' treatment wishes, reduction of decisional conflicts, improvement of documentation transparency and traceability, and reduction of the psychological and moral distress of a caregiver team. We also anticipate that the guideline will enable oncologists to make timelier and ethically informed treatment limitation decisions.

Methods

Design

This is a pre-post interventional design that analyzes the clinical practice of decision-making before and after the guideline implementation. The study consists of three stages: (1) the preinterventional phase (Time 1 [T1]; status quo), followed by the (2) intervention phase (development and implementation of the guideline; T2), and (3) the postinterventional phase (T3).

We use an embedded researcher design with a mixed-method approach that encompasses both qualitative and quantitative methods. We assume that using one research method is not sufficient to answer all of our research questions and that different methods are required. Embedded researcher design mixes different data sets at different design phases so that one data type provides a supportive, supplemental role or is embedded within other data types [12].

In phase 1 (T1), the current clinical practice of decision-making and documentation of decisions to limit treatment will be analyzed from three different perspectives: patients, their treating oncologists, and nurses. Phase 2 (T2) entails the development and implementation of a guideline on advanced care planning and limiting treatment. In phase 3 (T3), the impact of the guideline on the practice of decision making and documentation will be analyzed. The project outline is presented in [Table 1](#). This study protocol has been approved by the Ethics Committee of the Medical Faculty of the University of Munich.

Study Setting

The study is monocentric and is being carried out at the Department of Hematology & Medical Oncology at the University Hospital of Munich, Germany. A monocentric approach is being used, because the development of a guideline has proven to be more successful when it is developed within and for a particular location, taking into account specifics of the organizational context and of stakeholders' positions and professional self-conception of that environment [10].

Phase 1 (T1): Preimplementational Study of Current Decision-Making Practice of Limiting Tumor-Specific or Life-Prolonging Treatment

The first phase consists of three studies in which different methods are applied, with the aim to analyze the current state of decisions to limit a tumor-specific and life-prolonging treatment and to understand patients', oncologists', and nurses' needs regarding decisions to limit treatment. The insights from phase 1 will be used for development of the ethical guideline and for comparison with the results of phase 3 in order to detect any impact of the guideline after implementation in the pre-post comparison.

Table 1. Project outline.

Phases	Methods	Data collection	Sample/participants
Phase 1 (T1): Preinterventional phase – baseline survey	1. Embedded research	1. Documentation analysis	1. 500 patients' records
	2. Qualitative study	2. Semistructured interviews	2. 25 oncologists and nurses
	3. Quantitative survey	3. Questionnaire	3. 60 patients' cases (oncologists + nurses)
Phase 2 (T2): Intervention development and implementation of the ethical guideline	1. Group discussions with experts	N/A ^a	1. Oncologists, nurses, psycho-oncologists, external experts for palliative medicine, medical ethicists, medical law, ethics committee
	2. Several consensus conferences	N/A	N/A
Phase 3 (T3): Postinterventional phase – comparison with the results of phase 1 and evaluation	1. Embedded research	1. Documentation analysis	1. 500 patients' records
	2. Quantitative survey	2. Questionnaire	2. 60 patient's cases (oncologists and nurses)

^aN/A: not applicable.

Phase 1 includes: an observational baseline-survey on documentation, frequency, and timing of decisions to limit intensive medical care and tumor-specific therapy; a qualitative interview study with oncologists and oncology nurses; and a quantitative survey with patients, nurses, and oncologists.

Observational Baseline-Survey on Frequency and Timing of Decisions to Limit Intensive Medical Care and Tumor-Specific Therapy

As a first step of the preimplementational phase, we aim to examine how often decisions to limit treatment precede patients' deaths and how early they are determined. This baseline survey will enable us to investigate whether findings from the quantitative survey with oncologists, nurses, and patients are supported by observation and vice versa. The main research questions of the survey are presented in [Textbox 1](#).

For the observation, we will use a standardized documentation form. This form will be developed in a multi-step team process that will encompass literature review and discussions with experts including oncologists, palliative care physicians, medical ethicists, and social science experts. The documentation form will include the following information: patients' demographic data and diagnosis, the therapy/ intervention that have decided to be limited, how decisions to limit treatment are documented, changes in the scope of decisions to limit treatment, place of patient's death, therapy and medication 72 hours before patient's death, and whether decisions to limit treatment are followed or overruled in a patient's last days.

Textbox 1. Research questions.

- How often do decisions to limit treatment precede a patient's death?
- How often do patients die under chemotherapy or in the intensive care unit?
- How intensely are patients treated shortly before death?
- How well are decisions to limit treatment documented?
- How long before patients' death are decisions to limit treatment made?

Methods and Data Collection

We will use a method of an *embedded researcher* for this part of the project. The researcher is a member of a hospital team and participates in patients' sign-out reports from late to night shifts. She documents all treatment decisions made by oncologists. However, her role remains a passive one in order to avoid any influence on the current situation. If a patient dies, we will document all relevant decisions that preceded death. Furthermore, patients' transfer plans, charts, electronic hospital acts, and discharge letters will be analyzed.

Participants

All inpatients with advanced hematological/oncological neoplasia will be included if they are under treatment in at the Department of Hematology/Medical Oncology at the University Hospital in Munich.

Data Analysis

Data will be analyzed using Microsoft Excel.

Qualitative Interview Study With Oncologists and Oncology Nurses

In order to explore in-depth how oncologists and oncology nurses perceive treatment limitation decisions, a qualitative approach based on a grounded theory methodology will be used.

Methods and Data Collection

Qualitative individual face-to-face interviews will be conducted using a semistructured and pilot-tested interview guide. The interview topics are presented in [Textbox 2](#).

Textbox 2. Main interview topics.

- Treatment limitation situations
- Decision-making process
- Patients' involvement in decision-making
- Role of patients' family in decision-making
- Nurses' role in decisions to limit treatment
- Challenges and conflicts by decisions to limit treatment
- Oncologists' role in decisions to limit treatment

Procedure and Data Analysis

Purposive and theoretical sampling strategies will be applied. Participants are purposely sampled to represent different hospital units, working experience, age, and sex to reflect a wide range of opinions. The sampling will be continued until the theoretical saturation will be reached: when no new categories emerge and the relationships among categories are well-developed [13].

The collected data will be analyzed using the three-stage approach (open, axial, and selective coding strategies) of grounded theory methodology. MAXQDA software (VER BI GmbH, Berlin, Germany) will be used to assist with the coding and management of transcripts.

Quantitative Survey With Patients, Nurses, and Oncologists

In order to access and compare the perspective and reports of parties involved in decisions to limit treatment, we will survey patients, their respective oncologists, and oncology nurses. The survey will be complemented by a documentation form completed by a project researcher on each patient's case.

Patients' Survey**Development of the Questionnaires**

The study questionnaire will be developed based on a review of current literature and oncologists' and nurses' views and experiences derived from the interview study. A preliminary version of the questions will be checked by three experts (members of the research team) including an experienced psycho-oncologist, an oncologist with expertise in medical ethics, and a social scientist. We plan to use both established instruments as well as self-developed questions.

Established Instruments

The patients' questionnaire set comprises the questionnaire on: distress in Cancer Patients [14]; Whooley Depression Scale [15]; the perceived patients' quality of life, which will be

measured by a quality of life scale from European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 [16]; and the trade-off between patients' preferences for quality and length of life will be assessed with the Quality and Quantity Questionnaire [17]. We will translate and validate this questionnaire on a sample of advanced cancer patients within the scope of this project: the perceived role of patients' families in decision-making will be measured with the scale *Family Involvement in Treatment Decisions* from the validated German version of the Cancer Communication Assessment Tool for Patients and Families [18], and patients' roles in medical treatment decisions will be assessed with a German version of Control Preference Scale [19]. Satisfaction with a physician-patient interaction will be assessed using the validated questionnaire on the Quality of Physician-Patient Interaction [20]. We will use self-developed closed-ended questions with Likert scales to assess: patients' awareness of the treatment goal (curative or palliative); patients' recollection of discussing the treatment aim; patients' information needs regarding disease, prognoses, advance directives, and actual information received by patients; patients' communication preferences regarding treatment limitation; and satisfaction with decision-making.

Patient Recruitment

The inclusion criteria for patients are presented in [Textbox 3](#).

We will exclude patients with cognitive impairment and/or with a very poor general state of health. Patients will be recruited through a project researcher who will identify patients with decisions to limit treatment. In addition, oncologists will refer eligible patients when treatment limitation has been/is being discussed.

Patients will be recruited from five hospital units (n=5 normal wards) and the recruitment will take place until 60 patients with decisions to limit treatment are included in the study. All patients matching the inclusion criteria will be contacted by a project oncologist who will inform them about study aims and content.

Textbox 3. Inclusion criteria.

- Hospitalized cancer patients (male and female) over 18 years of age
- Diagnosed with advanced hematological/oncological neoplasia
- Decisions to limit treatment being either discussed or determined
- Adequate level of consciousness to complete the questionnaire
- Patients' agreement through an informed consent document

Table 2. Topics addressed in the questionnaire.

Assessed topics	Patients	Oncologists	Nurses
Cancer-specific distress	✓	—	—
Depression	✓	—	—
Information needs regarding disease (eg, prognosis, side effects, life expectation)	✓	—	—
Actual received information regarding disease	✓	—	—
Factors that influenced oncologists' decision of treatment limitation (eg, patients' age, quality of life)	—	✓	—
Estimation of patients' life expectation	—	✓	✓
Perceived (estimated) quality of life	✓	✓	✓
Information need for advanced directive/role of the advanced directive	✓	✓	✓
Discussed treatment limitation	✓	✓	✓
Planned or current treatment	✓	✓	✓
Level of difficulty of treatment limitation decisions	—	✓	—
Challenges that influenced treatment limitation	—	✓	✓
Consensus relating to treatment limitation decisions	—	✓	✓
Involvement of nurses in decision-making	—	✓	✓
Perceived aim of the treatment/estimation of patients' preferences regarding treatment limitation	✓	✓	✓
Discussion of the treatment aim/involvement of patients in decision-making	✓	✓	✓
Preference for quality or length of life	✓	✓	✓
Role in medical decisions	✓	✓	✓
Estimation of awareness of patients' prognosis	—	✓	✓
Satisfaction with oncologists' communication/communication with patients	✓	✓	✓
Perceived role of the family, wish for family involvement/involvement of family members	✓	✓	✓
Satisfaction with treatment decisions/consensus with oncologist	✓	✓	✓
Perception of optimal time for treatment limitation	—	✓	✓
Moral distress and its reasons	—	✓	✓
Support needs	—	✓	✓

Oncologists' and Nurses' Survey

Development of the Questionnaires

The oncologists' and nurses' questionnaire set will be developed as analogues to the patients' questionnaire to compare the answers to the same topics. In addition, we will assess moral distress in the care team with the Moral Distress Thermometer [21] and with two self-formulated open-ended questions on reasons for distress.

Furthermore, we will formulate questions to assess aspects such as: perceived difficulties by oncologists and nurses with decisions to limit treatment, oncologists' and nurses' satisfaction with decisions to limit treatment, and involvement of nurses in decisions to limit treatment. All topics that will be compared among oncologists, nurses, and patients are presented in Table 2.

Recruitment of Treating Physicians and Nurses at the Hematology/Oncology Inpatient Unit

For every patient's case the respective oncologist in charge and oncology nurse will be surveyed. The respective treating oncologist of the selected patients will be contacted and asked to participate in the study.

Data Analysis

Patients' characteristics will be evaluated using descriptive statistics. Patient cohorts will be formed based on patients' preference for length or quality of life, specificity of disease type (ie, oncological/hematological disease), type of therapy, and psycho-social variables. To compare the oncologists', nurses', and patients' views before and after guideline implementation, the Student t-test for paired data will be computed. Finally, linear regression analysis will be performed to identify possible predictors of oncologists' decisions to limit treatment and patients' involvement or noninvolvement in decision-making. Statistical significance will be assessed at the level of $\alpha=0.05$ (two-sided). All statistical analyses will be conducted using SPSS v.20.

Additional Documentation on Every Patient's Case

We will develop a special documentation form which will be completed by a project researcher on every patient's case, in addition to the quantitative survey. The aim of this form is to gather additional objective information regarding treatment limitation decisions. The researcher will complete the documentation form as soon as the patient has completed the questionnaire (date 1) and will proceed with documentation seven days later (date 2). If the decision has not been made yet, the documentation form will be filled approximately three days later, after date 2 once again (date 3).

Source of Information

The project researcher will screen patients' medical records to get necessary patient information. The documentation form will include information regarding hospital unit, patients' diagnosis and performance status (*Eastern Cooperative Oncology Group Performance Status*), patients' distress level at the time of hospital admission, pain information (numerical rating scale), type of therapy (eg, tumor-specific therapy [curative/palliative], anti-infective, radiation, parenteral nutrition, intravenous fluid substitution, transfusion, long-term medication for secondary diagnosis), and what additional supportive medication (eg, analgesics, sedatives) patients receive at the moment of documentation, as well as the availability of advance directives.

Additionally, the documentation form aims to assess other information, such as: patients' wishes regarding decisions to limit treatment, and if and where it is documented; if decisions to limit treatment have been made, and if and where they are documented; and, if a palliative consultation, if psycho-oncological consultation / support are offered and if social services are involved. All changes regarding treatment limitation in the next week will be noted as well.

Phase 2 (T2): Development and Implementation of the Guideline

The guideline will be developed in four interprofessional working groups with equal participation of clinic management, senior and assistant physicians, psycho-oncologists, nursing management, nurses, and quality managers. In group settings the participants will discuss different topics related to treatment limitation, communication, documentation of decisions, and legal aspects. Each group will formulate statements and recommendations which will be finally approved by the mandate holders that are eligible to vote. Finally, the guideline will be presented to the external experts of palliative medicine, medical ethics, and medical law for editing and improvement. The methodology of guideline development will be described in detail in a separate paper.

The Intervention

After presentation of the guideline at the internal hospital conference, mandatory training courses will be offered for oncologists and nurses to become familiar with the application of the guideline in their daily practice.

Phase 3 (T3): Postinterventional Study of Decision-Making Practice

After implementation of the guideline, all measurements from phase 1 (T1), aside from the in-depth qualitative interviews with oncologists and nurses, will be repeated to assess possible changes in clinical practice after guideline implementation.

Measure of Compliance to the Guideline

Oncologists' self-reported compliance to the guideline will be measured using several additional self-formulated questions on oncologists' guideline adherence that will be placed at the end of the questionnaire in phase 3. These questions will assess if the guideline will be used by oncologists in every patient's case and whether it will be helpful for end-of-life decision making. Furthermore, a short additional questionnaire is planned to assess oncologists' opinions on the applicability and practicability of the implemented guideline.

Results

Some parts of the project have been completed and published [17,22]. A qualitative study with 29 oncologists and oncology nurses revealed that participants had different approaches to initiation of end-of-life discussions. These approaches were ethically weighted and a framework for oncologists was elaborated. This framework favored an anticipatory approach of preparing patients for forgoing therapy throughout the course of disease [22]. The preimplementation study of current decision-making practice (n=567 patients documented) demonstrated that decisions to limit treatment preceded the death of many patients with a cancer disease (62/76, 82% of deceased patients), but usually were made in the last week of life [17].

Discussion

Overview

This paper describes the study design of an implementation and evaluation strategy of an ethical guideline for decision-making related to limiting treatment in advanced cancer patients that is grounded in empirical data. The pursued goal is to provide an informed, transparent, and ethically founded approach to controversial questions associated with treatment limitation, taking into account a specific environment of a university hospital.

As far as we are aware, this is the first study of its kind that uses a mixed-method approach, and involves patients, oncologists, and nurses to evaluate the impact of an ethical guideline on clinical practice. According to the literature review on institutional ethics policies for end-of-life decisions conducted by Lemiengre et al [23], most studies have focused on the implementation of do not-resuscitate policies; however, the use of before-and-after designs is scarce. Some studies deal with policies on pain, symptom control, and euthanasia [23]. However, there is a lack of pre-post interventional studies on ethical guideline development.

Study Strengths

Analysis of Different Perspectives

One major strength of this study is the evaluation of decision-making related to limiting treatment from different perspectives of oncologists, nurses, and patients, and comparing them to each other before and after implementation of the guideline. Additionally, we will analyze oncologists', nurses', and patients' needs and perceived difficulties in decision-making that will allow us to develop a guideline based on the interests of all parties. Furthermore, we will assess the perspective and needs of patients with advanced cancer shortly before dying. This patient group is not easy to include in studies as they are very weak and need a sensitive approach when they are assessed on end-of-life topics.

Mixed-Method Approach

An important strength of this study is the application of different methods and the collection of multiple sources of data (interviews, observations, and surveys) and perspectives of different parties (patients, oncologists, and nurses) to study the same topic. The triangulation of data contributes to the credibility of the results and will make the findings more grounded, thereby offsetting the weaknesses of both quantitative and qualitative research [12].

Multidisciplinary Team

For all phases of the project we will engage with a multidisciplinary team that includes experienced experts from psycho-oncology, sociology, clinical oncology, nursing, palliative medicine, and medical ethics. Decision-making at the end of life is a complex process that faces challenges of psychological, medical, and ethical natures. Different professional backgrounds and skills could provide a better framework for analysis and understanding of this process.

Study Limitations

One of the considerable limitations is a well-documented challenge that is associated with the pre-post interventional design studies. Pre-post studies assume that any difference in measurement in "prestudy" compared with "poststudy" is due to the intervention; however, they do not account for other

elements that are also changing at the same time that the intervention is taking place. It is difficult to determine if a certain intervention has indeed produced observed improvement.

A further limitation is that we have to use different patients' samples in pretests and posttests. The development and implementation of the guideline will take some time and many patients will not be available to participate in the posttest measurements. Furthermore, we must consider that by partaking in in-depth qualitative interviews and a very extensive questionnaire, the awareness of ethical issues among oncologists and nurses could be considerably raised. Consequently, it is difficult to distinguish the effects of the study itself on the clinical practice of decision-making from the effects caused by the guideline implementation. However, we should note that there is a high rate of fluctuation in a university hospital and this argument might not apply.

Additionally, the observed improvement could be due to the so-called Hawthorne effect (or observer effect) when participants change or adapt their behavior due to the awareness of observation and assessment [24]. This effect is not easy to quantify. However, literature suggests that triangulation of data using a variety of methods from different sources can contribute to reducing or even overcoming the mentioned effect [25,26]. A further limitation is related to certain particularities of a large university hospital setting. A characteristic of a university hospital environment is that junior staff at the wards rotate every 3-6 months. Consequently, some junior oncologists that participate in the preintervention phase may not have been present at the guideline implementation phase as well as at the postevaluation phase.

Conclusion

The results of this study aim at improving the development and implementation of ethical guidelines into clinical practice. We expect that our intervention will contribute to improvements in the decision-making processes on treatment limitation in patients with advanced cancer, increase the awareness for patient treatment preferences and their involvement in decision-making, and reduce psychological and moral distress within the caregiver team. Another expected outcome of the intervention is improvements in documentation transparency and traceability.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report (German).

[[PDF File \(Adobe PDF File\), 176KB - resprot_v7i6e157_app1.pdf](#)]

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Abbreviations

EPAL: Ethics Policy for Advanced Care Planning and Limiting Treatment

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Original Paper

Deception and Shopping Behavior Among Current Cigarette Smokers: A Web-Based, Randomized Virtual Shopping Experiment

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Abstract

Background: Virtual stores can be used to identify influences on consumer shopping behavior. Deception is one technique that may be used to attempt to increase the realism of virtual stores.

Objective: The objective of the experiment was to test whether the purchasing behavior of participants in a virtual shopping task varied based on whether they were told that they would receive the products they selected in a virtual convenience store (a form of deception) or not.

Methods: We recruited a US national sample of 402 adult current smokers by email from an online panel of survey participants. They completed a fully automated randomized virtual shopping experiment with a US \$15 or US \$20 budget in a Web-based virtual convenience store. We told a random half of participants that they would receive the products they chose in the virtual store or the cash equivalent (intervention condition), and the other random half simply to conduct a shopping task (control condition). We tested for differences in demographics, tobacco use behaviors, and in-store purchases (outcome variable, assessed by questionnaire) by experimental condition.

Results: The characteristics of the participants (398/402, 99.0% with complete data) were comparable across conditions except that the intervention group contained slightly more female participants (103/197, 52.3%) than the control group (84/201, 41.8%; $P=.04$). We did not find any other significant differences in any other demographic variables or tobacco use, or in virtual store shopping behaviors, including purchasing any tobacco ($P=.44$); purchasing cigarettes ($P=.16$), e-cigarettes ($P=.54$), cigars ($P=.98$), or smokeless tobacco ($P=.72$); amount spent overall ($P=.63$) or on tobacco ($P=.66$); percentage of budget spent overall ($P=.84$) or on tobacco ($P=.74$); number of total items ($P=.64$) and tobacco items purchased ($P=.54$); or total time spent in the store ($P=.07$).

Conclusions: We found that telling participants that they will receive the products they select in a virtual store did not influence their purchases. This finding suggests that deception may not affect consumer behavior and, as a result, may not be necessary in virtual shopping experiments.

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KEYWORDS

online shopping; deception; social and behavioral sciences; consumer behavior; smokers

Introduction

Virtual reality retail stores enable researchers to examine the real-time impact of changes in the retail environment on consumer behavior. Virtual store experiments can be used to understand the effects of changes such as store layout, product placement, advertising, and the presence of public health mass media campaigns on behaviors such as the type and number of products purchased and time spent in the store. Virtual stores provide a better method than static images on a computer screen of testing changes in the shopping environment [1] and offer the option of ensuring the feasibility of a business concept with a smaller investment of time and resources than would be needed for brick-and-mortar stores. Virtual supermarkets have also been used by researchers to solve problems in completing daily living skills among individuals with mental health problems and to assess cognitive functioning [2-4].

One persistent question in virtual store research is the degree to which the products that consumers select in the virtual store reflect the products they would select in a brick-and-mortar store or the products they actually want to purchase. A few studies have validated virtual store purchases with other shopping scenarios and have produced promising results. One such experiment used participant-provided receipts from supermarket purchases to validate virtual store purchases and found high levels of consistency between virtual and actual purchases [5]. Similarly, Desmet et al [6] found similar attitudes toward goods regardless of whether the good was viewed in a virtual or in a real store environment. However, purchase time, visual recall, and brand loyalty varied by store type. Similarly, the behaviors of 5 patients with schizophrenia who were completing shopping tasks in a virtual supermarket were comparable with their behaviors in real-life grocery stores [2]. van Herpen et al [1] found some differences between a virtual store and a physical store. However, shopping behavior was more similar between the virtual and physical stores than between static images of the virtual store and physical stores.

One aspect of research on virtual store experiments that remains unexplored is whether using deception in the instructions for the virtual store may improve the realistic nature of the virtual store (make virtual shopping experiences more closely resemble actual shopping experiences). Deception is a commonly used [7-9] (and sometimes necessary [10]) experimental method in marketing and consumer behavior research, psychology, and economics; however, its utility has never been tested in a virtual shopping experiment. We created a virtual convenience store, iShoppe, to understand the impact of the store environment on purchases, particularly tobacco product purchases. Previous experiments with iShoppe have informed research on the tobacco retail environment. For example, we found differences in attempts to purchase tobacco products based on whether a display of tobacco products was visible (open) or enclosed in a cabinet [11,12].

The objective of the experiment was to test whether the purchasing behavior of participants in a virtual shopping task varied based on whether they were told that they would receive the products they selected in a virtual convenience store (a form

of deception) or not. We varied the virtual store instructions for iShoppe to include deception or not. We hypothesized that we would find differences in virtual store shopping behavior based on whether the store instructions included deception or not.

Methods

Participants

Research Triangle Institute (RTI) International's institutional review board approved all study procedures. Between May 4 and May 11, 2015 (the time necessary for the quota of 400 participants to be reached), Lightspeed Online Research, LLC (Warren, NJ, USA), a market research company that provides data collection services for consumer research studies, recruited an online (invitation-only or closed) sample of adult current cigarette smokers living in the United States from their existing global panel of more than 5.5 million survey participants. Lightspeed recruits panel participants through email, internet ad banners, social media, e-newsletters, and referrals from recruiting partners.

Inclusion criteria for participation in the online-only randomized experiment were reporting living in one of the states in the United States, being the same age as or older than the tobacco minimum legal sales age for their state (18-21 years of age or older), and currently smoking cigarettes some days or every day (internet and computer literacy were also de facto inclusion criteria because the study was conducted online only). Exclusion criteria were not living in the United States, being under the tobacco minimum legal sales age for their state, and currently smoking cigarettes rarely or never.

Study Procedures

Potential participants were invited by email to complete an online screener (6 items on 6 pages) to determine their eligibility to participate in the voluntary study: "GlobalTestMarket is looking for your opinion. Don't miss out on being rewarded for sharing your opinions. Complete this survey today!" The email also contained a survey number, an offer of 100 "market points" (approximately US \$5 worth of points that could be redeemed for products and services from several corporate sponsors) for survey completion, and the URL for the screener. If participants met the inclusion criteria, they were provided a unique participant identifier (no identifying information was collected) and completed the informed consent. The consent invited them to click a checkbox to agree to complete the virtual shopping task in RTI International's iShoppe (developed in 2011 by a team of graphic designers at RTI International and software programmers, as part of a Robert Wood Johnson Foundation project in Research Triangle Park, NC, USA, using Unity 3D software; [Multimedia Appendix 1](#)) and, immediately afterward, a survey. In addition to the purpose of the study, the consent form included the number of participants recruited, risks and benefits of the study, information about incentives, confidentiality of the participants' responses, efforts to protect the participants and their privacy, information about the Unity 3D software program that must be downloaded as part of the study, and contact information for the project director and institutional review board.

After consenting, participants were randomly assigned to the intervention (deception) condition or the control (no deception) condition in a one-to-one (parallel) ratio (using a random number generator built into the software). All participants were aware that they were participating in a research study, but they were blinded to experimental condition (researchers analyzing the resulting data were not blinded to condition). After providing consent, participants were provided a link to the virtual store experiment, which began by providing directions that participants could purchase anything in the store (within a budget) and that, when done, they should click on the virtual clerk, who would help them complete their purchases. All participants had a budget of either US \$15 or US \$20. We assigned the higher budget to participants living in areas with higher excise taxes on cigarettes to ensure that all participants could afford to purchase tobacco products in the virtual store. In the intervention condition, we also instructed participants that, after completing the virtual shopping task, they would receive the products they selected from the virtual store by mail or, if the products were unavailable, the cash equivalent. We gave participants in the control condition no additional instructions. No alcohol products were available for purchase in the virtual store because some participants were under 21 years of age.

After completing the virtual shopping task, participants completed a short survey assessing their demographics and tobacco use (51 items on 51 pages). We developed all surveys (screener and postexperiment survey) based on literature reviews and, when possible, by using and modifying items from existing surveys. Surveys were tested by study staff and non-study staff employed by RTI International before fielding. Surveys contained skip patterns to reduce participant burden, but the order of the items was not random. Participants were required to complete all survey items (they could respond “prefer not to answer” or “don’t know”) before advancing to the next page or submitting the surveys. We analyzed only surveys with complete responses. Participants were able to log out and back in to the survey to accommodate participants unable to complete the experiment in one sitting. Speed checks were used to identify participants who completed the survey too quickly; however, no surveys were excluded for this reason.

At the end of the survey, during the debriefing, all participants were instructed that they would receive a Visa e-gift card for US \$20 (in addition to the Lightspeed incentive). Participants in the intervention condition were informed that they would receive the gift card in place of receiving the items they selected in the store by mail.

Variables

Descriptive Variables

We examined demographic and tobacco use variables across the intervention and control groups to characterize the sample and ensure that randomization was complete. Demographic variables, all of which were categorical, were age (≤ 34 years, 35-54 years, or ≥ 55 years of age); sex (male or female); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or non-Hispanic other); education (some high school

or less, high school graduate or General Education Development, some college, or college graduate or beyond, such as postgraduate or professional degree); and annual household income ($\leq \$25,000$, $\$25,000-\$49,999$, $\$50,000-\$74,999$, or $\geq \$75,000$ annually, all in US \$). Categorical tobacco use variables were number of days smoked in the past 30 (none, 1-2 days, 3-5 days, 6-9 days, 10-19 days, 20-29 days, or 30 days); ever daily smoking (yes or no); the last time the participant smoked (within the last hour, 1-2 hours ago, 2-5 hours ago, 5-10 hours ago, within the past day, or 2 days ago or longer); how soon after waking the participant usually smoked his or her first cigarette (≤ 5 minutes, 6-30 minutes, 31-60 minutes, or after 60 minutes); current smokeless tobacco use (yes or no); current use of cigars, cigarillos, or little cigars (yes or no); stopping smoking for 1 day or more in the past 12 months (yes or no); desire to quit smoking (not at all, a little, somewhat, or a lot); and planning to stop smoking in the next 30 days (yes or no). The only continuous variable was mean number of cigarettes per day smoked in the past 30 days. In addition, we examined the percentage of participants in the deception condition who reported that they understood that they might get all or some of the products that they selected in the store and that they might get a gift card in place of those products. Participants in the no deception condition were not asked this question.

Outcome Variables

The primary outcome variable, which was self-assessed online, was clicking to purchase any tobacco products. Secondary outcome variables were clicking to purchase cigarettes, e-cigarettes, cigars, or smokeless tobacco products (coded as 1 or more versus 0, the reference category), number of total items and tobacco product items purchased, dollars and percentage of the budget spent in total and on tobacco products only, and amount of time spent in the store.

Independent Variable

The independent variable was condition (intervention or control, reference).

Analysis

We used *t* tests for continuous variables and chi-square tests for categorical variables (or Fisher exact test as necessary for small cell sizes) to test for differences in demographics, tobacco use variables, and in-store behavior by condition. All analyses were completed at RTI International (Berkeley, CA office) in Stata 14 (StataCorp LLC), and significance was determined as a value of $P < .05$.

Results

Participants

Lightspeed contacted via email over 30,000 (32,588) members, of whom 2607 (8.00%) visited the screener site [13]. Of these, 402 (15.42%) completed the survey, 286 (10.97%) screened out, 9 (0.35%) attempted to complete the survey after the quota for participation had been reached, and 1910 (73.26%) either did not complete the screener or screened in but chose not to participate or did not complete the survey.

Table 1. Virtual store behaviors by experimental condition^a among participants who completed a virtual shopping experiment (n=398).

Outcomes	Experimental group		Total (n=398)	P value
	Control (n=201)	Intervention (n=197)		
Primary outcome (purchases), n (%)				
Any tobacco	124 (61.7)	114 (57.9)	238 (59.8)	.44
Cigarettes	115 (57.2)	99 (50.3)	214 (53.8)	.16
e-Cigarettes	14 (7.0)	17 (8.6)	31 (7.8)	.54
Cigars	3 (1.5)	3 (1.5)	6 (1.5)	.98
Smokeless tobacco	4 (2.0)	3 (1.5)	7 (1.8)	.72
Secondary outcomes, mean (SD)				
Amount spent in US \$	14.6 (3.9)	14.4 (3.5)	14.5 (3.7)	.63
Percentage of budget spent	86.9 (19.0)	87.3 (18.5)	87.1 (1.9)	.84
Amount spent on tobacco products in US \$	5.4 (5.2)	5.1 (5.2)	5.2 (5.2)	.66
Percentage of budget spent on tobacco products	31.9 (30.0)	30.9 (30.7)	31.4 (30.3)	.74
Number of items purchased	5.9 (3.2)	5.8 (2.7)	5.9 (3.0)	.64
Number of tobacco product items purchased	0.9 (0.9)	0.8 (0.9)	0.9 (0.9)	.54
Total time in store (minutes)	5.0 (3.9)	5.7 (3.9)	5.3 (3.9)	.07

^aParticipants in the intervention (deception) condition were told that they would receive the products that they selected in the virtual store by mail (or the cash equivalent if the products were unavailable). Participants in the control (no deception) condition were told they would receive the cash equivalent of the products they selected.

Only 46.99% (1225/2607) of those who clicked on the link finished the first page of the screener. Of the 402 participants, 398 (99.0%) provided complete data (Multimedia Appendix 2 shows the flow diagram of the selection process). Reporting of the methods and results of this study complies with the CONSORT-EHEALTH guidelines (Multimedia Appendix 3) [14].

Descriptive Statistics

Overall, participants were predominantly white with high levels of education and income (Multimedia Appendix 4). More than half were daily smokers, and almost all had ever smoked daily. Almost half had smoked within the last hour, more than half usually smoked within a half hour of waking, and about one-quarter reported current use of smokeless tobacco. One-third of participants reported current use of cigars, cigarillos, or little cigars. About one-third had made a quit attempt in the past 12 months, one-third wanted to quit smoking “a lot,” and 68.3% (272/398) planned to stop smoking in the next 30 days. Mean number of cigarettes smoked per day was 16.0 (SD 14.1). Among participants in the deception condition, 77.2% (152/197) reported that they understood that they would receive the products they selected (or some of them) or a gift card.

Analysis

The control condition had slightly fewer female participants than the intervention condition ($P=.04$). There were no other significant differences in demographics or tobacco use behaviors between conditions.

Results of Analysis

The percentage of participants who purchased any tobacco products did not vary by condition ($P=.44$; Table 1). Also, there

was no difference by condition in the percentage of participants who purchased specific types of tobacco products, including cigarettes ($P=.16$), e-cigarettes ($P=.54$), cigars ($P=.98$), and smokeless tobacco ($P=.72$). The total amount of money spent ($P=.63$), percentage of budget spent ($P=.84$), and number of items purchased ($P=.64$) did not vary by intervention condition. Similarly, the amount spent on tobacco products ($P=.66$), percentage of budget spent on tobacco products ($P=.74$), and number of tobacco product items purchased ($P=.54$) did not vary by condition. Total time spent in the store was slightly longer in the intervention condition than in the control condition, but this difference was only marginally significant ($P=.07$).

Discussion

Principal Findings

We found no significant differences in the purchasing behavior of participants in this virtual shopping experiment (for overall purchases or tobacco-specific purchases) based on whether we told them that they would receive the products they selected (ie, using deception) or not. This finding suggests that deception does not affect the products that participants select in a virtual store.

No previous study, to our knowledge, has examined the impact of deception on purchasing behavior in a virtual store experiment. Our results suggest that deception may not make the virtual store more believable, that is, more likely to reflect consumer preferences (the products that consumers actually want to purchase). Our results are consistent with several research studies that found no differences between experimental conditions that contained deception and those that did not. Barrera and Simpson [15] conducted a classic prisoner’s

dilemma study with sociology students at a large university. Participants in the treatment condition were told that they had a partner who was involved in the decision-making task but were afterward told that no partner existed, while participants in the control condition were assigned a real partner. The researchers found no difference in the behavior of the participants in the prisoner's dilemma task across conditions. Similarly, a review found that, in previous studies involving deception, there was no difference in the experimental behavior of participants who were and were not deceived. Only when participants were explicitly told before the study that they would be deceived or were intentionally made suspicious of the purpose of the study by experimenters did their behavior differ [16].

Although the literature has not examined the role of deception in virtual stores, existing research has found that virtual stores provide valid information on actual shopping behavior. Using a consumer panel recruited by phone in the Netherlands, van Herpen et al [1] randomly assigned participants to a physical store, a virtual store, or to view screenshots of the virtual store, then compared the products they selected for purchase across the three conditions. For all conditions, participants were reimbursed with gift certificates (E van Herpen, electronic communication, February 2018). Researchers confirmed that, after the experiment, all participants in the physical store condition used their gift certificates to purchase (in the same physical store) the products that they had selected during the experiment. They did not compare the products that participants in the virtual store or screenshot conditions selected to those same participants' later purchases in real stores. van Herpen et al [1] found that participants in the virtual store and screenshot conditions purchased more products and a greater variety of products than participants in the physical store condition. However, purchases of participants in the virtual store condition more closely resembled the purchases of participants in the physical store condition than they resembled the purchases of participants in the screenshot condition. Waterlander et al [5] recruited adults in New Zealand using print and online

advertising and found some differences in the amount of money spent on food groups between the virtual store and participant-provided receipts. However, the 4 food groups with the highest relative expenditures were the same for the virtual stores and receipts. Taken together, these results suggest that virtual stores are likely to be a valid method of assessing shopping behavior.

Limitations

Based on the findings of this analysis alone, we cannot definitively conclude that deception is not needed in virtual store research. First, it is possible that unmeasured confounders explain the nonsignificant difference in shopping behavior by condition; however, randomization lessens this possibility. Second, we cannot be sure that deception was successful. Although we know that most participants in the deception condition understood that they would receive the products (or some of them) and that they might get a gift card instead of the products, it remains unclear how many of them believed they would receive the products (as opposed to the gift card). One potential explanation for the lack of differences in shopping behavior by condition is that neither group believed that they would receive the products they selected. It also remains unclear whether respondents' in-store shopping behavior would have been different had we promised to give them the products they selected immediately after they completed the experiment (which was not possible because the study was administered online), as opposed to saying we would mail them the products at a later date. Given these limitations, the results of this analysis should be interpreted with caution.

Conclusion

The purchasing behavior of virtual shoppers did not vary based on whether or not they were told that they would receive the products they selected in the virtual store. The results of this study suggest that deception about the receipt of goods following a virtual shopping task is unlikely to affect consumer behavior in virtual stores.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Screenshots of the iShoppe virtual convenience store.

[[PDF File \(Adobe PDF File\), 1MB - resprot_v7i6e10468_app1.pdf](#)]

Multimedia Appendix 2

Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

[[PDF File \(Adobe PDF File\), 14KB - resprot_v7i6e10468_app2.pdf](#)]

Multimedia Appendix 3

CONSORT-EHEALTH checklist (V 1.6.1).

[[PDF File \(Adobe PDF File\), 746KB - resprot_v7i6e10468_app3.pdf](#)]

Multimedia Appendix 4

Demographic characteristics and tobacco use behavior by experimental group among participants who completed a virtual shopping experiment (n=398).

[[PDF File \(Adobe PDF File\), 30KB - resprot_v7i6e10468_app4.pdf](#)]

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Abbreviations

RTI: Research Triangle Institute

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Protocol

Important Design Features of Personal Health Records to Improve Medication Adherence for Patients with Long-Term Conditions: Protocol for a Systematic Literature Review

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Abstract

Background: The National Health Service (NHS) England spent £15.5 billion on medication in 2015. More than a third of patients affected by at least one long-term condition do not adhere to their drug regime. Many interventions have been trialed to improve medication adherence. One promising innovation is the electronic personal health record.

Objective: This systematic literature review aims to identify the important design features of personal health records to improve medication adherence for patients with long-term conditions.

Methods: This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P 2015) statement. The following databases will be searched for relevant articles: PubMed, Science Direct, BioMed Central, Cumulative Index to Nursing and Allied Health Literature, Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials. Studies published in the last fifteen years, in English, will be included if the participants are adults who were treated outside the hospital, have the ability to self-administer their medication, and have at least one long-term condition. The review will exclude commercial or political sources and papers without references. Papers that research pediatrics, pregnant, or terminally ill patients will also be excluded, since their medication management is typically more complex.

Results: One reviewer will screen the included studies, extract the relevant data, and assess the quality of evidence utilizing the Grading of Recommendations Assessment, Development, and Evaluation system and the risk of bias using the Cochrane RevMan tool. The second reviewer will assess the quality of 25% of the included studies to assess interrater agreement. Any disagreement will be solved by a third reviewer. Only studies of high and moderate quality will be included for narrative synthesis.

Conclusions: NHS policy assumes that increasing usage of personal health records by citizens will reduce demand on health care services. There is limited evidence, however, that the use of health apps can improve patient outcomes, and, to our knowledge, this is the first systematic literature review aiming to identify important design features of the personal health record which may improve medication adherence in the adult population with long-term conditions.

Trial Registration: PROSPERO CRD42017060542; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=60542 (Archived by WebCite at <http://www.webcitation.org/6zeuWXxVh>)

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KEYWORDS

personal health records; medication adherence; chronic condition; comorbidities; drug regime; long-term conditions

Introduction

The annual National Health Service (NHS) England spend on medication was £15.5 billion in 2015 and the volume of medication prescribed in by NHS England rises every year [1-3]. The World Health Organization (WHO) reported that the average medication adherence in patients with long-term conditions in developed countries is approximately 50% [4]. According to the WHO, there is a need to acquire more data related to medication adherence from all age band subgroups [4]. It is estimated that, in the UK, more than a third of patients with at least one long-term illness do not adhere to their medication regime [5]. Medication nonadherence is associated with higher number of hospitalizations, adverse drug reactions, nursing home admissions, and an increase in health care and social costs [6].

A number of systems are currently employed to use information and communication technologies (ICT) to store, manage, and employ health and medical information. The use of ICT for NHS health care policy was made clear in the 2002 report, *Securing Our Future Health: Taking a Long-Term View* [7], even though patients' electronic access to their health records had already been planned in *The NHS Plan 2000* [8]. Following that, the NHS developed the Summary Care Record and HealthSpace programs to explore the development and application of shared electronic health records (EHRs) and personal health records (PHRs) [9]. The NHS Future Forum highlights the importance of patient access to their online GP health records to assist in the development of a self-care and self-management culture [10].

NHS policy documents and frameworks such as the *Personalised Health and Care 2020* (P2020) report [11] and the *Five Year Forward View* [12] specify that the NHS needs to harness the power of technology. The aim is to enable patients to make correct choices and to support clinicians by providing access to all necessary data and assisting the clinicians to make the most of technology available and these data. The P2020 claims that unless the gap between care and technology closes, patients may experience "unnecessary levels of preventable ill health" [11]. It also provides evidence of the growing demand for technology in England, as evidenced by the fact that 59% of all UK citizens have a smartphone. It also compares the health care sector to other safety-critical industries and it argues that digital tools and technologies, such as mobile apps, improve self-management of patients' health [11].

There are four main terms in general use for structured health care information systems, namely electronic medical records (EMRs), electronic patient records (EPRs), EHRs, and PHRs [13]. Although there have been attempts to differentiate the definitions of EMR, EPR, and EHR [14-16], in practice, these terms lack precision and are often used interchangeably [13]. We have adopted the term "EHR" in this protocol. The definition of a generic EHR is "a repository of information regarding the

health status of a subject of care, in computer processable form" [13,17].

There are multiple definitions of a PHR. Generally, the term "PHR" emerged from "EHR" and can be defined as "health records related to patient care that are controlled by the patient" [18]. Although there are paper based PHRs, in this protocol we refer to PHRs that are electronic and accessible via mobile devices [18].

Based on the PHR definitions provided by Cruickshank [9], Paton [19], Rohers [18], and Archer [20], we identified the common denominators and the following PHR definition is used throughout this protocol and the systematic literature review:

PHRs are online systems that include collections of patients' health care and medical data, which utilize health informatics standards to enable patients to share, organize, and manage these data according to their own views. [21]

This definition is agnostic to the type of PHR, which can be defined as tethered [16,20,22] or standalone [18,20]. A tethered (tied) PHR includes features that are not patient-controlled; thus, it can be connected to the data source, including the cloud and institutional EHRs [16,18,20]. Untethered or standalone PHRs' main feature is that the patient-user is the only one permitted to enter, maintain, and self-manage data related to their own health conditions [20,23]. Based on the above definition, this review will also include studies that use copies of personal health data on storage devices, such as smart cards and USB sticks. Figure 1 illustrates how the EHR and PHR differ for health care and medical records.

PHRs are typically important for patients that are suffering from chronic conditions, whom gain the most value from the PHR and have a higher adoption rate for PHR use [20,24-26]. Some PHR characteristics, as derived by the literature [20,24-26], are summarized in Table 1.

The adoption of PHRs is global, for example, PHRs are expected to be adopted by 75% of patients in the USA by 2020 [27]. In Australia, a national tethered PHR system has been launched [28] and in Canada and Denmark there are health centers which offer PHRs to their patients [9]. Furthermore, the NHS England is working toward a greater adoption of PHRs [11,12,29]. There is a growing focus on the adoption of PHRs worldwide because, in addition to geographically targeting the major economies such as the USA and UK, studies have also been conducted in middle- and low-income countries to evaluate, improve, and quantify the benefits of PHR use in global health [9,30-35].

The scope of this review is global and there are no geographical restrictions on this study. The use of PHRs not only varies between different groups of patients, but it also varies among studies [36]. Patients that have a long-term condition or an illness that requires recurrent care are more likely to use a PHR than patients who claim to be in good health [37]. The adoption of PHRs worldwide started around 2003 [9], so all the evidence

is recent, and this remains an immature and rapidly developing field. Illustrating this, early in 2011 Google decided to terminate

their PHR product (Google Health) due to its low impact and adoption rate [9,38].

Figure 1. Description of the differences and concepts between electronic health records (EHRs) and personal health records (PHRs) [15,18]. GP: general practitioner.

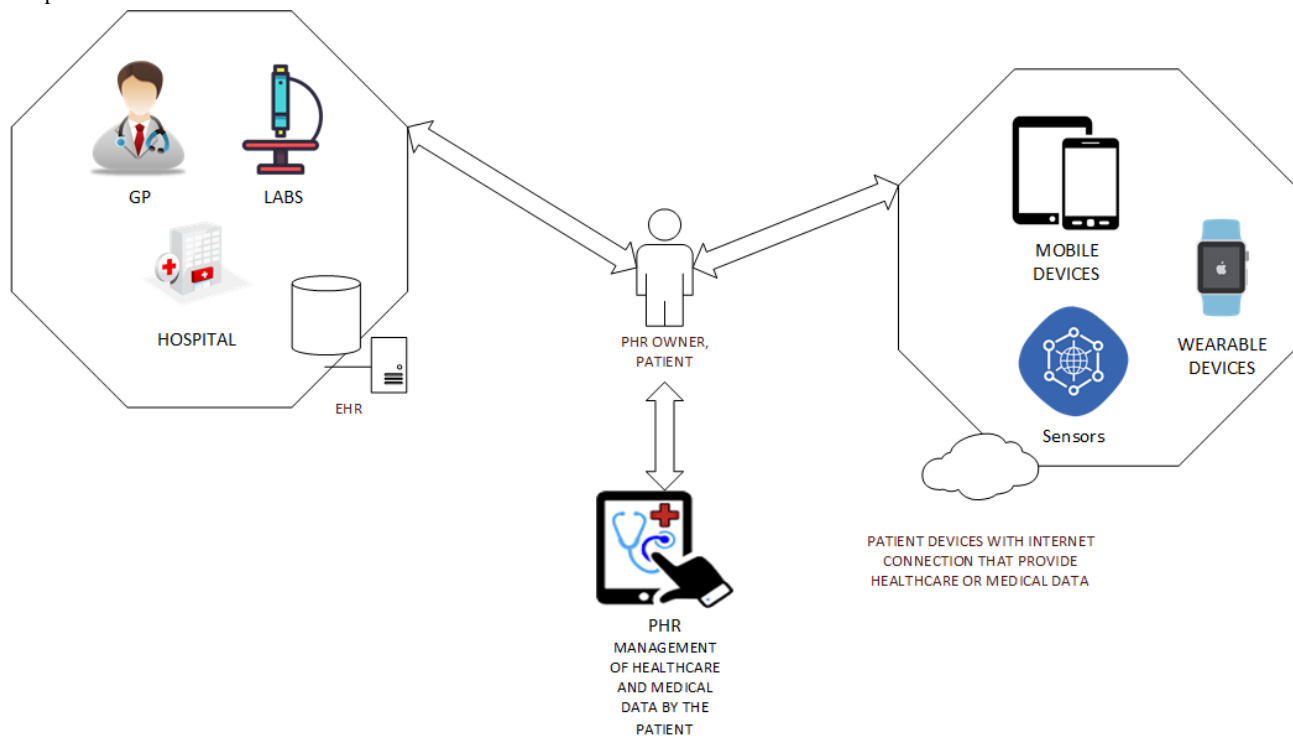


Table 1. Summary of personal health record (PHR) characteristics as derived by the literature [20,24-26].

PHR Characteristic	Examples
Administrative	Booking appointments, paying bills
Clinical features	View lab test results, view prescriptions, add medical history
Online access	May provide access to electronic health record data
Managed by patient	The patient’s data are controlled by patient
Data repository	Organizing health information, documenting symptoms, documenting medication dosages
Improves communications	Between patients and/or patient-doctor
Personalization	Provides individualized and tailored clinical information to patients
Medication adherence reminders	Might be alarms or text messages etc

NHS England engaged in a “landscape review” in 2015 to identify how local NHS organizations and commercial companies are using PHRs [39]. Most research and quality of life and care schemes that the NHS is currently referencing have been published after 2011 [11,36,40,41]. This context has informed our selection of a suitable date range for the literature searches.

There are many claimed benefits of PHRs, such as (1) the ability of PHRs to improve patient outcomes, (2) decrease in care costs, (3) to give patients the ability to self-manage their health, (4) an increase access to care especially in remote areas, (5) empowerment of patients, and (6) to improve medication adherence [18-20,24-26,36,42,43].

Medication adherence can be defined as “the extent to which a person’s behavior towards their medication intake, corresponds with agreed recommendations from a health care provider” [44]. Medication adherence is the preferred terminology, but some sources still use the word “compliance,” which many consider to be dated as it is a more restrictive term and less patient centered [45]. The ABC taxonomy [46] was selected as the conceptual framework for medication adherence in this study since it is well cited, it includes the time dimension, and it is considered more comprehensive than the WHO five interacting dimensions that affect adherence [44]. The ABC taxonomy states that there are three components to medication adherence: initiation (the time until the first dose has been taken), implementation (the extent to which a patient’s dosage consumption corresponds to the prescribed dose regimen) and

discontinuation (stop taking the medication) [46]. Medication adherence and persistence are closely related and often persistence is incorporated in the notion of adherence [46,47]. Medication persistence can be defined as the extent to which patients adhere over time [45], in other words it is the time between the medication initiation until the medication discontinuation [46]. According to some authors, medication compliance and medication adherence are synonymous [46], with the latter not only to be introduced as a less aggressive term to describe the same phenomena but also to provide the patient with a sense of self-control and self-management of their treatment [48,49]. Concordance is another important term related to adherence to prescribed medication, which reflects the need to reach an agreement between a patient and the prescriber by which health beliefs are accounted for. A concordant consultation would be expected to lead to enhanced adherence to medication, as the prescribing process would involve the patient in the clinical decision making [48].

Some studies indicate that polypharmacy has a negative effect on medication adherence [44,50,51]. Polypharmacy is defined as the parallel use of multiple medications by one patient, for complex or multiple conditions [52-54]. Polypharmacy can signify “the prescribing of either many drugs (appropriately)” or “too many drugs (inappropriately)” [55]. Our focus extends to either use of polypharmacy, since the impact of PHRs on either polypharmacy or simple prescribing is unknown.

Medication adherence is a well-known challenge in health care [44,56-58], and is related to a large number of factors such as side effects [59], forgetfulness [57], or effective self-management and is affected by psychological factors and beliefs [60]. Although a number of strategies and interventions have been identified to assist patients’ medication adherence [58,61], they have had limited success.

Table 2. Summary of the PICOS elements (participants, interventions, comparators, outcomes and study design) included and excluded in the systematic review.

Variable	Inclusion criteria	Exclusion criteria
Participants	<ul style="list-style-type: none"> • Humans • Adults with at least one long-term condition • Patients that can self-administer their medication • Patients that are able to communicate freely and able to self-manage their medication • Patients treated outside the hospital only 	<ul style="list-style-type: none"> • Animals • Pregnant, cancer, or terminally ill patients • Adults with medically serious problems that are not classified as long-term conditions • Patients that require assistance with taking their medication • Patients unable to communicate or unable to self-manage their medication. • Inpatients or patients living in care homes
Intervention	Interventions of any type, intensity and frequency, that aim to investigate the effect of electronic PHRs ^a in medication adherence, concordance, compliance or persistence.	N/A ^b
Comparators	N/A	N/A
Outcome	Any outcome related to the effect of electronic PHRs in medication adherence, concordance, compliance or persistence	N/A
Study design or type	Studies or literature reviews published in the last fifteen years, without any geographical restriction	Abstract-only reports without any references, commercial studies, party political statements, general discussion papers, magazine or newspaper articles, withdrawn abstracts or articles, protocols of reviews

^aPHR: personal health record.

^bN/A: not applicable.

NHS policy assumes that increasing the usage of health apps by citizens will reduce demand on health care services. However, the quality of the literature about the use of health apps to improve patient outcomes is often questionable [62].

Aim and Objectives

The aim of this systematic review is to identify important design features of the electronic PHR that may improve medication adherence in the adult population with long-term conditions.

Primary Objective

The primary objective of this systematic review is to identify the important design features of the electronic PHR which may improve medication adherence in the adult population with long-term conditions.

Secondary Objectives

- Identify the PHR design features that improve medication adherence in the cases of:
 - Polypharmacy;
 - Specific long-term condition groups;
- Identify if there is a correlation between participants’ demographic characteristics, their usage of PHRs, and their medication adherence;
- Explore how implementation factors affect the outcomes.

Methods

This protocol complies with the requirement of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P 2015) including the PICOS elements (participants, interventions, comparators, outcomes and study design) highlighted in Table 2 [63].

Search and Selection Strategy

High heterogeneity of the data is expected, in terms of target diseases, interventions, outcome measures, and study types. Therefore, a meta-analysis is avoided in favor of a qualitative analysis. A narrative synthesis [64] of the peer-reviewed medical and nursing literature as indexed in PubMed/MEDLINE, PubMed Central, Association for Computing Machinery digital library, Emerald Insight, Science Direct, BioMed Central, and Cumulative Index to Nursing and Allied Health Literature will be undertaken. The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials will also be searched and any abstract-only reports without any citations will be excluded. Additional papers derived manually from the reference lists of the selected articles or studies, as well as from Research Gate and Google Scholar during the screening process, will also be included. Conference proceedings will also be searched using the Web of Science and IEEE Xplore databases. Discovery services from ProQuest will be used to include theses and dissertations on the search. All published studies, as described above, reported during the past fifteen years will be considered. Two reviewers (EA, PJS) will screen the included studies.

Papers in English will be considered for this review. The studies selection will be managed using Mendeley Desktop v 1.17.9 and Mendeley Web.

The search strategy was developed iteratively, based on trial searches, using the PICOS framework [63], together with a university librarian, and takes into consideration the methods section of previous systematic literature reviews in the field. The search strategy used is:

(phr OR "personal health record" OR "patient portal") AND adult AND ("chronic disease" OR "chronic illness" OR "chronic condition" OR "long term disease" OR "long term illness" OR "long term condition") AND ["medication compliance" OR "medication adherence" OR "medication concordance" OR "medication persistence"]*

The search includes the following MeSH [65] terms: personal health records, medication adherence, and chronic disease.

The strategy does not include the terms "p.h.r." nor "P.H.R.," since these terms obscured the preliminary results by adding an unnecessary load of marketing and human resources related results, which are clearly out of the scope of this research. The search terms of the strategy were combined with Boolean Operators (ie, "AND" and "OR"). During preliminary searches, the word PHR was replaced by the words "medication record" or "medication profile" based on pharmacist advice; this search yielded very similar results in PubMed Central and, in fact, excluded 2 studies. A search that initially seemed promising was including the word "medication" and the word "adherence" by themselves (ie, "medication" AND "adherence"). A similar preliminary search excluded the word medication altogether. These two searches yielded tens of thousands of hits, which initially seemed promising, but, upon inspection, it was apparent that either the papers were investigating PHRs as recreational software, commonly for depression and weight loss, or the

papers were investigating PHRs in conjunction with adherence to general therapeutically regimens such as weight loss and gym attendance.

Participants

As illustrated in Table 1, the inclusion and exclusion criteria for the participants are the following. Studies that include adult patients with any long-term disease and use any type of self-administering medication will be assessed for inclusion. For this review, adult is defined as ≥ 18 years of age.

Studies that include adult patients with cancer, who are terminally ill, pregnant, or have any other problems which make patients unable to communicate freely and self-manage their medication will be excluded. Studies that include only inpatients or care home residents will be excluded.

Intervention

Interventions researching influences which affect patient medication adherence will be included in this review as described in Table 1. Included studies will include interventions of any type, intensity, and frequency, which aim to investigate the effect of PHRs on medication adherence, compliance, persistence, and concordance.

The interventions may initially be grouped as:

- Interventions that explore the effect of PHR on medication adherence [44,46,66], compliance [45,46], persistence [66], and concordance [45];
- Interventions that explore how and how much patients use PHRs and the effect this use might have in medication adherence, compliance, persistence and perceptions;
- Interventions that explore the notion of polypharmacy in adult patients with multiple conditions and how PHRs and technology in general may be of assistance.

Outcome

The primary outcome of the studies included in the review is medication adherence. However, medication adherence, compliance, persistence, and/or concordance are complicated terms to measure and often depend on the authors' point of view, background, and the authors' definitions of the above terms [48]. Furthermore, there is often a confusion surrounding the differences between the terms, for example, the difference between medication adherence and persistence [56]. Due to this complexity, an inclusive approach will be used to determine the outcomes of the included studies.

Data Extraction

The data extraction forms were created based on the National Institute for Health and Care Excellence data extraction forms [67] and the data extraction chapter from the Cochrane Collaboration [68]. In cases of missing data on the PICOS elements, an email will be sent to the authors of the study. If there is no response within two weeks, a second email will be sent, and if there is still no response from the authors, the study will be excluded. The data extraction forms were designed to collect all the data needed to address the review questions and to follow the data synthesis strategy. The forms were piloted

on a random selection of 10 of the included studies to assess any potential issues ([Multimedia Appendix 1](#)).

The following information will be extracted from each study:

1. Basic study characteristics (eg, title, authors, journal, abstract, keywords, publication, aim)
2. Study design and study period
3. Population characteristics (eg, age, number of participants, chronic illness etc)
4. Intervention characteristics (eg, length of use, design features, technological characteristics, vendor of PHR, type of PHR)
5. Outcome measures (eg, self-reported, clinical outcomes, medication adherence ideal)
6. Outcomes (eg, primary and secondary outcomes involving medication adherence, quality of life, and polypharmacy)

Besides the above data, additional information will be documented for the quality assessment and risk of bias analysis, as described below.

Quality Assessment and Risk of Bias

Each eligible study will be assessed for validity and quality of evidence, using the Critical Appraisal Tools written by The Joanna Briggs Institute [69]. If there are studies that are eligible for inclusion, but have missing data, the authors of these studies will be contacted to see if these data can be obtained and used in this review.

Each eligible study will also be assessed for risk of bias using the Cochrane handbook 2011 [70]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool [71] will be used to assess the quality of the aggregate evidence for each outcome, based upon five factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence will be rated as high, moderate, low, or very low for every outcome.

The main reviewer (EA) will evaluate all the included studies, the second reviewer (PJS) will evaluate 25% of the included studies and interrater reliability will be calculated [72]. Any disagreement will be solved by consulting a third reviewer. Only studies of high and moderate quality, as defined by GRADE [73], will be included in the review.

Data Synthesis and Analysis

Based on the aim of this review, the wide range coverage of research designs, multiple interventions and outcomes, as well as the expectation of high heterogeneity, all the data that will be extracted from the studies will be analyzed narratively using an interpretative framework [64,74]. To ensure that the narrative analysis will be of good quality, the “Guidance on the Conduct of Narrative Synthesis in Systematic Reviews” [64] will be followed, which is in line with the Cochrane data synthesis and analysis guidelines [74].

The narrative analysis will attempt an investigation into the similarities and the differences between the outcomes of different studies and an exploration of themes (patterns) in the data. The guidelines [64,74], include the following four stages of a narrative synthesis in reviews:

1. Development of a theory of how the intervention works, why, and for whom. The initial theory and the familiarization with the data will be achieved based on the development of a textual description of the studies, which will be produced systematically including, where possible, the same information for all studies and in the same order [64].
2. Development of a preliminary synthesis of the findings of the included studies. The preliminary synthesis will be developed using a tabular analysis of the studies in multiple tables, using Microsoft Excel, followed by a thematic analysis, which will systematically identify the recurrent themes across the included studies [64].
3. Exploration of the relationships in the data between and within studies. A conceptual model will be developed to explore relationships in the data, which will group similar findings and identify relationships between these groups, providing visualization of the possible relationships across studies [64].
4. Assessment of the robustness of the synthesis. A Best Evidence Synthesis (BES) approach will be followed. BES is typically applied during the selection process and is primarily concerned with the methodological quality of the included studies. BES guidelines require that all the included studies will meet the minimum standards for relevance and quality of evidence, and that all the extracted data will be systematically extracted based on the data extraction forms. Therefore, the decision regarding the “strength of evidence” will be made early in the review process [64].

The analysis will be conducted in an iterative and abductive way and the results will be thoroughly discussed with the other two authors (PJS and HH).

Potential Amendments

There is no intention to amend the protocol; thus, the possibility of outcome reporting bias will be reduced. However, if any amendments are needed during the review process, they will be clearly and comprehensively reported.

Results

There is no requirement for ethical review since this study is secondary research. The final report of the systematic review in the form of a scientific paper will be published in a peer-reviewed journal. Findings may further be presented at conferences and be submitted to relevant NHS authorities. We also plan to include an updated version of this systematic review in the author’s thesis.

Discussion

This research is limited to include only articles that have outcomes related to the effect of electronic PHRs in medication adherence, concordance, compliance, or persistence, rather than also including other outcomes such as quality of life. In this sense, the review will focus exclusively on articles that measure medication adherence as a primary or secondary outcome. This review is limited to obtain articles published either in ICT or

health care and medical portals. This means that a lot of ICT related literature is unobtainable, since it is not included in the academic literature, but is commercial or governmental work. The aim of this review is to identify the essential design features

of the PHR that assist adults with at least one long-term condition to adhere with their medication, without taking into consideration adolescents nor adults that are not considered chronically ill or terminally ill, have cancer, or are pregnant.

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Authors' Contributions

EA designed the protocol, drafted the manuscript, and is the guarantor of the review. PJS revised the manuscript multiple times for methodological and intellectual content. HH revised the manuscript twice for methodological, conceptual and intellectual content from a pharmaceuticals perspective. The final version of the manuscript was approved by all three authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Data extraction forms.

[[PDF File \(Adobe PDF File\), 25KB - resprot_v7i6e159_app1.pdf](#)]

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Abbreviations

EHR: electronic health record

EMR: electronic medical record

EPR: electronic patient record

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICT: information and communication technologies

P2020: Personalised Health and Care 2020

PHR: personal health record

PICOS: participants, interventions, comparators, outcomes, and study design

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

WHO: World Health Organization

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Protocol

Integrating Electronic Patient-Reported Outcome Measures into Routine HIV Care and the ANRS CO3 Aquitaine Cohort's Data Capture and Visualization System (QuAliV): Protocol for a Formative Research Study

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Abstract

Background: Effective antiretroviral therapy has greatly reduced HIV-related morbidity and mortality, dramatically changing the demographics of the population of people living with HIV. The majority of people living with HIV in France are well cared for insofar as their HIV infection is concerned but remain at risk for age-associated comorbidities. Their long-term, potentially complex, and growing care needs make the routine, longitudinal assessment of health-related quality of life and other patient-reported outcomes of relevance in the current treatment era.

Objective: We aim to describe the development of a Web-based electronic patient-reported outcomes system for people living with HIV linked to the ANRS CO3 Aquitaine cohort's data capture and visualization system (ARPEGE) and designed to facilitate the electronic collection of patient-reported data and ultimately promote better patient-physician communication and quality of care (both patient satisfaction and health outcomes).

Methods: Participants who meet the eligibility criteria will be invited to engage with the Web-based electronic patient-reported outcomes system and provided with the information necessary to create a personal patient account. They will then be able to access the electronic patient-reported outcomes system and complete a set of standardized validated questionnaires covering health-related quality of life (World Health Organization's Quality of Life Instrument in HIV infection, named WHOQOL-HIV BREF) and other patient-reported outcomes. The information provided via questionnaires will ultimately be presented in a summary format for clinicians, together with the patient's HIV care history.

Results: The prototype of the Web-based electronic patient-reported outcome system will be finalized and the first 2 formative research phases of the study (prototyping and usability testing) will be conducted from December 2017 to May 2018. We describe the sequential processes planned to ensure that the proposed electronic patient-reported outcome system is ready for formal pilot testing, referred to herein as phases 1a and 1b. We also describe the planned pilot-testing designed to evaluate the acceptability and use of the system from the patient's perspective (phase 2).

Conclusions: As the underlying information technology solution, ARPEGE, has been developed in-house, should the feasibility study presented here yield promising results, the panel of services provided via the proposed portal could ultimately be expanded and used to experiment with health-promoting interventions in aging people living with HIV in hospital-based care or adapted for use in other patient populations.

Trial Registration: ClinicalTrials.gov NCT03296202; <https://clinicaltrials.gov/ct2/show/NCT03296202> (Archived by WebCite at <http://www.webcitation.org/6zgOBArps>)

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KEYWORDS

patient-reported outcomes; HIV; patient-centered care; health-related quality of life; patient-generated health data

Introduction

Background

The advent of effective antiretroviral therapy (ART) in 1996 in resource-rich settings led to a sharp and rapid decline in AIDS-related deaths [1]. In the following years and now decades, improved treatment options have normalized the survival of people living with HIV (PLWH) [2]. For PLWH to benefit fully from ART, they must be engaged in the continuum or cascade of HIV care. In other words, they must be diagnosed early, linked and retained in care, and receive and adhere to effective therapy [3]. The Joint United Nations Programme on HIV and AIDS' 90-90-90 targets aimed at ending HIV as a public health threat by 2030 are premised on this continuum of care [4]. They call for diagnosing at least 90% of people living with HIV, getting at least 90% of those who are diagnosed on ART, and achieving viral suppression in at least 90% of those who are treated. In settings where the 90-90-90 targets have already been achieved, Lazarus and colleagues have argued that the ultimate goal of HIV care should be to improve health-related quality of life (HRQoL) and have thus proposed a fourth 90%: "achieving good health-related quality of life among 90% of those who are successfully treated for HIV" [5].

This fourth 90% reflects the current needs of the population of PLWH in much of Western Europe, including France, where HIV has become a chronic condition over the most recent decade. The 2013 French HIV Treatment Guidelines first called for addressing the health of PLWH as understood by the World Health Organization, meaning as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [6]. The concept of HRQoL comes from this definition of health and has become especially relevant to those living with a chronic or recurrent illness.

HRQoL is a common patient-reported outcome (PRO). PROs may be used at the population level for research and to improve health care quality and at the individual patient level to support clinical decision-making and ensure the efficient use of resources. However, despite these potential benefits to both clinicians and patients, PROs have yet to be routinely collected or systematically used in routine care by clinicians [7]. This is due to logistical, methodological, and attitudinal barriers [7]. Some of the first studies on the use of PROs in clinical practice have yielded mixed results. There is strong evidence that having patients complete a self-assessment before a medical visit can

facilitate communication about HRQoL [8-13]. Yet, the body of evidence on whether this type of exercise alters patient management, affects outcomes, or improves HRQoL or satisfaction is less well understood [14]. Greenhalgh et al have pointed to the lack of theory-driven approaches used to evaluate the use of PRO measures in routine clinical practice and propose that the mechanisms by which the proposed intervention is hypothesized to affect patient outcomes be clearly delineated [15]. Others like Basch et al have argued that the proliferation of robust survey methods coupled with computerized technologies has provided a potentially viable means of collecting this information and ideally integrating it into electronic medical records (EMR) [16]. Computerized and touch-screen technology can substantially facilitate data collection compared with paper forms, eliminating data-entry and scoring time, and therefore decrease staff burden. Yet, often EMRs and clinical research database systems have been designed to allow for data entry from study staff, making the collection of PROs challenging in some care or research settings [17].

In the context of HIV cohort research, The University of Washington HIV Cohort was among the first to experiment with the routine computerized collection of patient-based measures. Crane et al described efforts to institute the routine collection of electronic PROs (ePROs) in HIV care, concluding that it was both promising for research and clinical care [18]. Whereas Kozak et al highlighted some of the challenges of capturing high-quality data in routine care and the limitations of data recorded in patients' paper medical or EMR [19]. They note that the demands of clinical care and patients' willingness to disclose sensitive information may compromise the comprehensiveness and the quality of data captured via EMRs. In their 2012 study, conducted at the University of Alabama at Birmingham 1917 HIV/AIDS clinic, they compared self-reported and EMR data and looked at the association between substance abuse, depression, and poor ART adherence in PLWH. Not only did authors document significant differences in the prevalence of self-reported vs EMR-documented substance use and depression, but they found that the self-reported rather than EMR-documented measures were better correlated with poorer ART adherence [19]. This research suggests that ePRO are an alternative and potentially more reliable means of data capture for sensitive domains such as substance use. Furthermore, ePROs may help clinicians identify problems at the time of care, as demonstrated by Lawrence et

al [20]. As part of the same initiative at the 1917 HIV/AIDS Clinic, ePROs were used to detect suicidal ideation and trigger an automated page to predetermined clinic personnel who completed more detailed self-harm assessments [20].

Objectives

This paper outlines the formative research protocol being undertaken to develop a Web-based system to collect ePROs linked to the existing data capture infrastructure for those in HIV care in southwestern France. The first aim of the ePRO system is to expand and improve the data collection for the ANRS CO3 Aquitaine Cohort of PLWH being followed up in the 13 public hospitals in the region. The second aim is to make this information available to clinicians in a convenient format together with patients' locally developed, HIV-specific EMR. We describe the sequential process planned to ensure that the proposed ePRO system is ready for formal pilot testing, referred to herein as phases 1a and 1b. We also describe the planned pilot testing designed to evaluate the acceptability and use of the ePRO system from the perspective of patients (phase 2). We have outlined the hypothesized changes induced by the inclusion of these data in a locally developed HIV-specific EMR, which is currently being developed.

Methods

Study Designs

The ANRS CO3 Aquitaine cohort is an open, prospective hospital-based cohort. The proposed research was conceived as an ancillary study to the cohort. This protocol reports on the sequential study design from the prototyping (phase 1a) and usability testing (phase 1b) to piloting (phase 2). Phases 1a and 1b rely on mostly qualitative methods. Perspectives of the patient will be assessed and barriers to and facilitators of implementation identified through usability testing. The second phase of the research will initially be based on a cross-sectional study design with the ultimate aim of collecting these data longitudinally (at least once a year) and systematically via the revised ePRO system.

Platform Design

Clinical and laboratory data from medical records have been collected systematically as part of routine care by a team of clinical research associates/technicians from 13 clinics/hospitals throughout the Aquitaine region since the 1980s and via a locally developed information technology (IT) solution, ARPEGE, since 2013. ARPEGE is a secure Web-based data capture and visualization system developed with Microsoft ASP.NET (WebForm). Data are stored within a Microsoft SQL Server 2014-based data management system. A responsive Web-based platform has been designed for patient follow-up within the existing infrastructure of the ANRS CO3 Aquitaine Cohort. This IT solution was originally developed to meet the data collection requirements of the ANRS CO3 Aquitaine Cohort. Unlike the hospital's EMR, which did not allow for data to be visualized nor used for research, ARPEGE provides HIV physicians with patients' medical histories. Its interoperability with the surrounding health information system infrastructure has evolved to allow laboratory data to be downloaded from

the Bordeaux University Hospital's laboratory medicine information system, which includes results of all tests performed as part of hospital-based care. The proposed QuAliV ePRO system expands upon this IT solution by developing a flexible interface for the Web-based collection of ePROs both in a hospital setting and beyond (in the patient's home) with a special focus on the presentation of individual patient's results. The inclusion of administrative data from the Program for Medicalizing Information Systems and clinical data from the hospital's EMR is planned but has not yet been completed.

Initial Website Specifications

The primary feature of the ePRO system is the survey feature due to the platform being nested within a longstanding hospital-based cohort study. The first feature is to facilitate data collection on HRQoL and its main determinants via validated electronic questionnaires. The content of the patient interface is based on current treatment guidelines for people being treated for HIV and associated comorbidities [6]. French guidelines recommend an annual checkup, during which a number of issues should be addressed by the HIV physician according to the patients' age and sex. According to the taxonomy of applications of PROs in clinical practice laid out by Greenhalgh, the proposed system aims to optimize this checkup by having the patient complete a standardized self-reported questionnaire before the visit [10]. The proposed ePRO system relies on a selection of validated questionnaires that were mostly already available in French. The questionnaires have already been evaluated individually according to their psychometric properties, administration method, and length. The following areas are covered by the ePRO system, broken up into thematic modules covering: socioeconomic status and individual social and material deprivation (Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé [EPICES]) [21], multidimensional quality of life (WHOQOL-HIV BREF) [22], treatment burden (Treatment Burden Questionnaire) [23], physical activity (The Short Version of the International Physical Activity Questionnaire [IPAQ]), alcohol use and screening for at-risk drinking behavior (Alcohol Use Disorders Identification Test Consumption [AUDIT-C], Fast Alcohol Consumption Evaluation [FACE]) [24], tobacco and nicotine use and screening for tobacco dependency (Fagerström), cannabis (Cannabis Abuse Screening Test [CAST]) and drug use, and finally, depression (Patient Health Questionnaire [PHQ-9]) [25]. The system also allows patients to report any other treatment-related issues in a free-text field. Where applicable, we have followed the recommendations put forth by the International Society for Pharmacoeconomics and Outcomes Research ePRO Task Force on adapting paper-based instruments to ensure that data produced are equivalent or superior to those generated from paper-based administration methods [26]. It should be noted that the choice of questionnaires for the initial prototype is intentionally more exhaustive than the anticipated final version, as we do not know whether the questionnaires selected will be adequate in terms of their psychometric properties. This will be verified during the pilot phase.

We have planned additional IT security measures including the encryption of email addresses using the Advanced Encryption Standard encryption algorithm with a key length of 256 bits.

Advanced Encryption Standard encryption technology is currently one of the most secure. Passwords will be encrypted by the BCrypt algorithm, which is recognized as being at the cutting edge of hash chain technology. Furthermore, passwords created by the user must contain at least 8 alphanumeric characters including at least 2 special characters, a capital letter, and a number that must be changed every year. The unique study-specific identification number will contain 8 randomly defined alphanumeric characters.

Preimplementation (Phases 1A and 1B)

The IT solution, ARPEGE, has been made available in hospital-based HIV care centers since 2013. Its use is facilitated by research assistant technicians. To inform the implementation strategy, taking into account the facilitators and barriers faced by users, a preimplementation assessment identifying those factors crucial to implementation success or failure will be conducted before determining the final implementation procedure.

Phase 1A: Prototyping (Eliciting Feedback on Initial Specifications)

On the basis of the above specifications, a preliminary version of the interface will be constructed and presented to patients to elicit their feedback. The aim of the preliminary qualitative interviews is not to rigorously evaluate the website's performance but to obtain information that could be used to develop the interface and prepare it for formal pilot testing. Using a semistructured interview guide, we will interview a convenience sample of 10 HIV patients of varying ages, transmission groups, and genders. During the interview, the interviewer will present a mock-up of the Web-based patient interface and describe its proposed functions to each participant.

Phase 1B: Usability Testing

Usability measures to what extent a person can use a system for its goal effectively, efficiently, and satisfactorily [27]. Usability testing will be conducted on the prototype of the ePRO system according to guidelines from the website Usability.gov [28]. A convenience sample of 10 patients will be recruited and interviewed in an outpatient hospital setting. This sample is considered adequate to evaluate whether the website is ready for planned, more rigorous, pilot testing [29]. Eligible patients, identified by clinical staff, will be approached for the study before their scheduled visit. During usability testing, patients will access the website and test its features, including the site login, survey completion, and review of results. Patients will "think aloud" as they complete the login process and survey and complete a semistructured interview about the ease of use and completion, presence of mistakes or problems, user satisfaction, likes/dislikes, and their willingness to use it regularly before visits. Efficiency (eg, time it takes to complete tasks) will also be monitored. Finally, participants will also be asked to complete the System Usability Scale (SUS), a validated 10-item scale with Likert-scaled responses ranging from "strongly agree" to "strongly disagree" and a summary score [28].

The findings from this first phase (1a and 1b) will inform the second phase of the study, which will extend the implementation of the proposed patient interface in a limited number of hospitals and aims to evaluate its acceptability and use.

Phase 2: Pilot Testing

Proposed Setting

The study will be carried out in the ANRS CO3 Aquitaine Cohort, an open, prospective, hospital-based cohort of PLWH followed-up in 13 clinics in southwestern France. The pilot testing will take place in 3 of them, selected to reflect variations in resources (human and material) or geographic setting (rural vs urban clinics). We aim to assess the acceptability of the proposed system in different clinical contexts to eventually offer center-specific adjustments to the proposed implementation procedures.

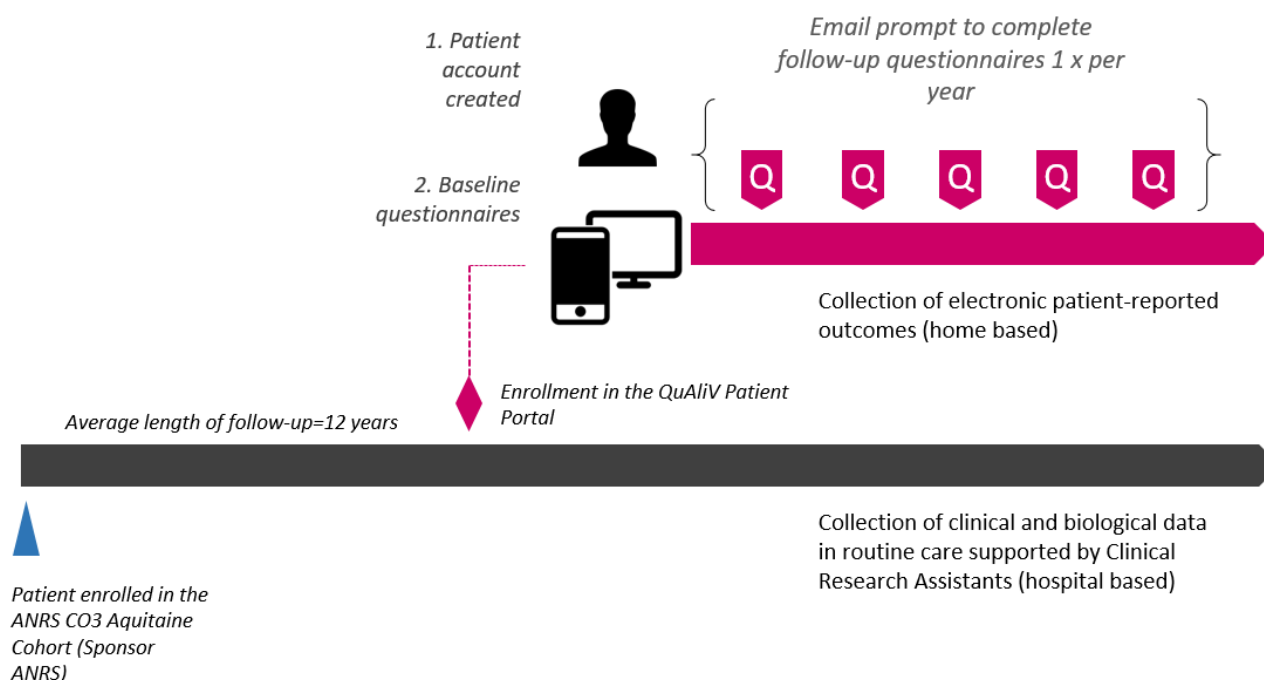
Inclusion and Exclusion Criteria (Phase 2)

As this study will be nested within a longstanding existing hospital-based cohort of PLWH, those invited to participate in this study must meet the cohort's eligibility criteria: aged 18 years or older, confirmed HIV-1 diagnosis, and having signed a consent form. Access to a personal email account and the internet via either a computer or smartphone in a private setting will be verified by the clinician before the participant is invited to engage with ePRO system. Patients who express an interest in completing a self-reported questionnaire but lack either a personal computer or smartphone and/or reliable internet access will be provided with a paper version questionnaire or, depending on the study center, invited to use a study-specific electronic tablet (Samsung Galaxy Tab S2).

Patient Selection and Recruitment

Patient selection and recruitment will be done in tandem with planned administrative changes to the cohort and will take place during routine care. The standard operating procedures detailing the new procedures for including participants in this component of the cohort have been developed during successive team meetings. Before each visit, on-site research assistants will provide clinicians with a study-specific randomly generated patient identifier. Clinicians will invite patients to participate in the ANRS CO3 Aquitaine cohort's new research initiative at the time of the consultation. Figure 1 outlines the integration of the QuAliV patient portal in the ANRS CO3 Aquitaine Cohort.

Once the eligibility criteria have been verified, if the patient wishes to participate in the study, he/she will be provided with a patient-oriented brochure developed specifically for those interested in engaging with the system. The study-specific identifier required for participants to create their accounts will then be noted on a detachable part of the patient-oriented brochure for easy reference. This study-specific identifier is required to create an account via ARPEGE. It allows for the patient account and the self-reported data to be linked to the existing clinical data capture and visualization system (ARPEGE).

Figure 1. Integration of the QuAliV patient portal in the ANRS CO3 Aquitaine Cohort.

As the patients could be accessing the website from their phones or from their home computers, the section of the brochure for noting the study-specific identifier will be detachable, allowing the study participant to leave the brochure at the hospital for the sake of confidentiality (Multimedia Appendix 1). To monitor study enrollment and ascertain whether the proposed system is acceptable to users, enrollment will be tracked by the centers.

Eligible participants will be directed to the study website where they will be provided with additional details about the research initiative and its aims. The website will provide additional information to “recruited” patients, encouraging them to take a more active role in his or her HIV care and well-being. The patient will be redirected to the account creation page, powered by ARPEGE. To ensure that the participant created his/her account successfully, he/she will be asked to enter his/her email twice together with the unique patient identifier. The patient will then be asked to confirm his/her email address before he/she can access the patient portal. Metadata will be monitored to identify any bottlenecks during the pilot phase.

Study Population

The cohort’s “active follow-up” is defined as patients who have been seen over the course of the previous year either at a hospital-based consultation or been hospitalized. In 2016, approximately 4480 patients were actively being followed-up in the cohort. The average length of follow up is 12 years post HIV diagnosis. In total, 27.95% (1252/4480) of the cohort is female and mean age is 51 years (SD 11 years). The majority of the cohort contracted HIV through sex (41.93% (1881/4486) are men who have sex with men and 37.09% (1664/4486) are heterosexuals) and 12.75% (572/4486) through injection drug use. Moreover, 20.60% (923/4480) of those in active follow-up have been diagnosed with AIDS, 26.70% (1010/3745) are overweight, and 8.62% (323/3745) are obese. In addition, 43.71% (1831/4189) report being current smokers.

Statistical Analysis

Feedback on initial specification from patients will be evaluated qualitatively during phase 1a. During phase 1b, in addition to qualitative feedback provided using the “think aloud” approach and semistructured interview, we will define success in usability a priori as SUS score reaching a ceiling effect: with a minimum score of 70 as the generally accepted cutoff usability rating for “good” [27]. For each measure, we will also calculate the percentage of completed items by the total number of items for each PROs module.

We will monitor eligibility, QuAliV numbers issued, accounts created, and initial questionnaires completed within 1 month of the visit. The following process indicators will be used to assess acceptability:

- The proportion of people who refused to participate in the study
- the proportion of those who received information but failed to create an account
- The proportion of those who created an account but failed to complete the questionnaires

To assess use, the main outcomes of interest of the phase 2 study are the overall participation rate (proportion of those who created an account and completed the assessment) implemented as a pilot and the participation rates based on readily available personal, demographic, and treatment-related factors. Differences based on age, sociodemographic characteristics (including rural vs urban), and clinic and transmission groups will be evaluated using the chi-square test. Determinants of use will be evaluated using logistic regression methods.

As all the questionnaires will be used in an electronic form, the psychometric properties of the instruments included in the patient portal will also be verified. We will be especially attentive to the presence of floor and ceiling effects (60% of

responses in extreme categories). We will also monitor the time it takes to complete the questionnaire as a further indicator of feasibility. The dimension of HRQoL measured by the instruments will be assessed using confirmatory factor analysis.

Finally, we will use the pilot phase to verify the distribution of the main outcome of interest (HRQoL) of our epidemiological study, seeking to measure both the prevalence and the determinants of poorer HRQoL in PLWH in the current HIV treatment era. We will use this initial sample to calculate the required sample size and plan for the scale up of the platform in all of the participating hospitals/clinics in the region.

Ethical and Legal Aspects

The implementation of this study called for an amended version of the cohort protocol to be submitted to an ethics committee. This amendment entailed a detailed description of the content of the questionnaires included in the ePRO system, the content of patient-oriented brochure and the external patient-oriented website. Approval was granted in August 2017.

As the implementation of this system requires patients to use their email addresses to create their personal accounts, an amendment to the regulatory authorizations previously granted to the cohort by The French National Commission on Informatics and Liberty, an independent administrative regulatory body charged with ensuring that data privacy laws are applied to the collection, storage, and use of personal data, was requested in late 2017 and approval was granted on March 12, 2018.

Results

Seed funding was granted by France REcherche Nord&Sud Sida-hiv Hépatites (ANRS) in 2017 via the CSS-5 call in January, 2017 and additional staff recruited in June 2017 to develop the ePRO system's infrastructure. DB was awarded a 36-month "young researcher" grant from Sidaction to design and conduct this study within the ANRS CO3 Aquitaine cohort as part of her doctoral research.

The development of the prototype of QuAliV ePRO system and the first 2 phases of the study will be conducted between December 2017 and May 2018. The results from phase 1 will ultimately inform the implementation of the pilot project. Efforts to integrate data generated from the ePROs system into a HIV-specific EMR will begin in April 2018 as part of the next phase of APREGÉ's development. Enrollment of participants is planned in June 2018.

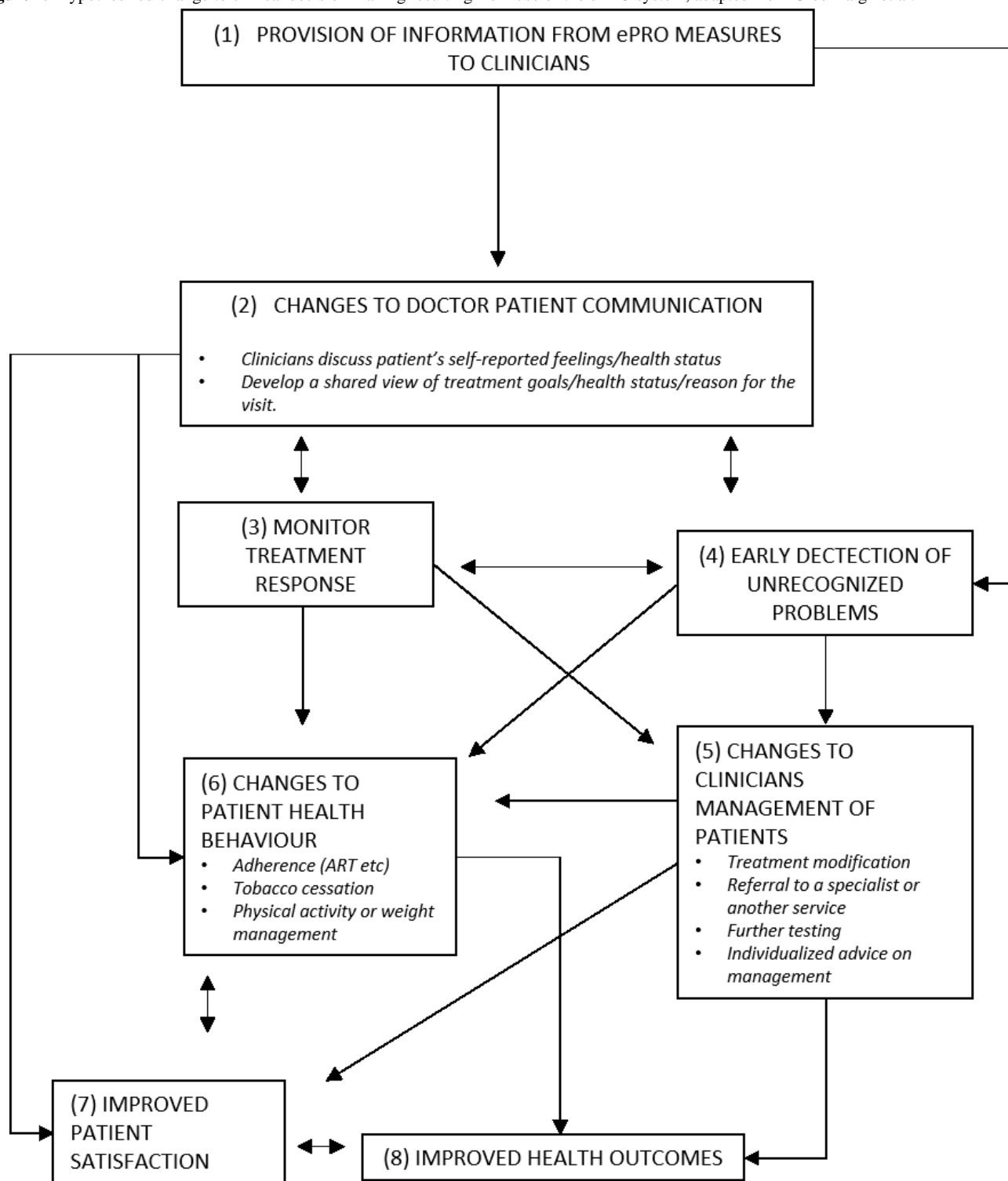
Discussion

Although France boasts a robust public health and epidemiological surveillance system, its cohorts relied, until

recently, on paper-based data collection methods. The Aquitaine cohort, launched in 1987, transitioned to an electronic Case Report Form supported by center-based clinical research technicians in 2013. The relatively recent transition to an electronic data capture and visualization system has made the collection of ePROs in hospital-based cohort studies of PLWH conceivable and timely in light of the current HIV care paradigm in France. The introduction of the proposed ePRO system and updated physician HIV-specific EMR, presenting a summary of patients' clinical, laboratory, and self-reported records, will imply changing both patient behavior and daily clinical practice.

In line with recommendations put forth by Greenhalgh and colleagues, we have diagrammed the hypothesized mechanisms by which this patient ePRO system is designed to promote improved patient-physician communication (Figure 2, adapted from Greenhalgh et al) [15]. The results of the self-reported questionnaires will be summarized for clinicians in a convenient format developed in collaboration with end users. We hypothesize that providing this information can improve communication and, thus, lead to better quality of care (both patient satisfaction and health outcomes). Presenting this information will also allow HIV physicians to monitor the patient's response to treatment over time (ART and treatment for associated comorbidities) and/or detect issues that may have previously gone unnoticed (eg, a change in employment status, living conditions, addictions, a lack of social support, depression, and/or a decline in HRQoL). We hypothesize that physicians will also be better equipped to discuss health-promoting behaviors such as exercise or smoking cessation, adjust treatment regimens, or refer patients to a specialist or allied health professionals (eg, therapist, dietician, social worker).

As the underlying IT solution, ARPEGE, was developed in house, should the phases 1a and 1b and phase 2 studies, presented here, yield promising results, the panel of services provided via the proposed ePRO system could ultimately be expanded. For example, continuous patient education/coaching for better self-management, similar to interventions that have been implemented for other chronic conditions (diabetes, heart disease, etc), could be offered, as could decentralized models of care and/or facilitated communication with one's general practitioner. The adoption of these different services could ultimately be the aim of future experimental research in this patient population aging with HIV. Alternatively, the proposed system, designed for outpatient hospital-based HIV care, could be adapted for use in other chronic diseases and/or other care settings.

Figure 2. Hypothesized change to clinical decision making resulting from use of the ePRO system, adapted from Greenhalgh et al.

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Conflicts of Interest

DB has received a speaking fee from Gilead. FB declares to have received reimbursement for attending a symposium from ViiV Healthcare, Gilead, Bristol-Myers Squibb, Merck and Janssen; speaking fee and consultancy fee from ViiV Healthcare, Gilead, Bristol-Myers Squibb, Merck and Janssen; and funds for research from Gilead and ViiV Healthcare. The other authors do not have any conflicts of interest to declare.

Multimedia Appendix 1

Patient-oriented brochure with detachable coupon.

[[PNG File, 478KB - resprot_v7i6e147_app1.png](#)]

Multimedia Appendix 2

Conclusions of External Peer-review (English Translation).

[[PDF File \(Adobe PDF File\), 323KB - resprot_v7i6e147_app2.pdf](#)]

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Abbreviations

ART: antiretroviral therapy
EMR: electronic medical records
ePRO: electronic patient reported outcome
HRQoL: health-related quality of life
PLWH: people living with HIV
PRO: patient-reported outcome
WHO: World Health Organization

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Original Paper

The General Practitioner Prompt Study to Reduce Cardiovascular and Renal Complications in Patients With Type 2 Diabetes and Renal Complications: Protocol and Baseline Characteristics for a Cluster Randomized Controlled Trial

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Abstract

Background: Adherence to evidence-based cardiovascular risk factor targets in patients with type 2 diabetes and microalbuminuria has shown long-term reduction in mortality and morbidity. Strategies to achieve such adherence have been delivered at individual patient level and are not cost-effective. Health care professional-level intervention has the potential to promote better adherence at lower cost.

Objective: The aim of this study was to assess the effectiveness of a multifactorial technology-driven intervention comprising health care professional training, a software prompt installed on practice systems, clinician email support, and enhanced performance and feedback reporting.

Methods: A cluster randomized trial will be performed where the primary outcome is the proportion of eligible patients meeting tight cardiovascular risk factor targets, including systolic and diastolic blood pressure (BP; BP<130/80 mm Hg) and total cholesterol (TC; TC<3.5 mmol/L) at 24 months. Secondary outcomes include proportion of patients with glycated hemoglobin (HbA_{1c}) <58 mmol/mol (7.5%), change in medication prescribing, changes in microalbuminuria and renal function (estimated glomerular filtration rate, eGFR), incidence of major adverse CV events and mortality, and coding accuracy. Cost-effectiveness of the intervention will also be assessed.

Results: Among 2721 eligible patients, mean age was 62.9 (SD 10.0) years, and duration of diabetes was 10.46 (SD 7.22) years. Mean HbA_{1c} was 59.3 (SD 17.4) mmol/mol; mean systolic and diastolic BP (mm Hg) were 134.3 (SD 14.6) and 76.1 (SD 9.5) mm Hg, respectively; and mean TC was 4.1 (SD 0.98) mmol/L. Overall, 131 out of 2721 (4.81%) patients achieved all 3 “tight” cardiovascular risk factor targets. Cardiovascular risk factor burden increased two-fold in those with eGFR<60 mL/min/1.73 m² compared with those with eGFR≥60 mL/min/1.73 m². Prevalence of microalbuminuria was 22.76%. In total, 1076 out of 2721 (39.54%) patients were coded for microalbuminuria or proteinuria on their primary care medical record.

Conclusions: The general practitioner prompt study is the largest UK primary care-based, technology-driven, randomized controlled trial to support intensive intervention in high-risk group of multiethnic individuals with type 2 diabetes and microalbuminuria. This paper provides contemporary estimates for prevalent cardiovascular disease and adherence to evidence-based cardiovascular risk factor targets at baseline in a population with type 2 diabetes and microalbuminuria. The main trial results, including cost-effectiveness data, will be submitted for publication in 2018.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN14918517; <http://www.isrctn.com/ISRCTN14918517> (Archived by WebCite at <http://www.webcitation.org/6zqm53wNA>)

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KEYWORDS

diabetes mellitus, type 2; primary health care

Introduction

Type 2 Diabetes and Microalbuminuria

Microalbuminuria (MA) in patients with type 2 diabetes (T2DM) is associated with a significantly increased risk of cardiovascular (CV) mortality and related morbidity [1]. Current evidence advocates targeted, tight, multiple risk factor control to reduce CV risk [2]. Recent audit data suggest that despite current guidance, over 80% of patients with MA and T2DM do not meet all treatment targets for blood pressure (BP), total cholesterol (TC), and glycated hemoglobin (HbA_{1c}) [3].

Evidence for Tighter Cardiovascular Risk Factor Control

Previous studies have demonstrated the effectiveness of patient-level interventions using tighter treatment targets [4,5] including group patient education [3,6], showing long-term beneficial microvascular and macrovascular benefits in addition to reduced mortality.

Strategies to improve quality of care in diabetes, including health care professional (HCP) education, providing financial incentives, professional reminders, and audit and feedback, have generally reported improvements in care, albeit with modest reductions in HbA_{1c} [7]. Due to differences in interventions, outcome measures, and study populations, it is difficult to compare data on effectiveness between clinician- and patient-focused interventions [8].

Although there is evidence to suggest that patient-level interventions to manage CV disease (CVD) are cost-effective [9], questions loom over the ability to implement them with limited resources available in primary care settings. Simple prompts integrated into existing information technology (IT) systems to identify patients during routine consultation, in combination with education for clinicians, may serve as an “aide-mémoire” and provide an opportunity to improve standards of care at low cost [10-12]. More specifically, it has been shown to improve adherence to medication in studies targeting a reduction in CVD risk in people with T2DM [13,14]. The provision of patient “reminders” and audit and feedback are facilitated through existing practice IT systems [15]. This highlights opportunities for intervention in patients at the time of clinical encounter [16] and is effective in improving HCP behavior to achieve patient risk factor targets [15].

The General Practitioner-Prompt study

The general practitioner (GP) prompt study was designed to test the hypothesis that a multifaceted, multifactorial intervention in patients with T2DM and MA aimed at primary care HCPs

aided with an electronic “Prompt” would result in a selective, intensive, and targeted intervention of CV risk factors in these high-risk individuals and an increase in the proportion meeting tight multiple CV risk factor targets [2].

Methods

Study Design

This study is a pragmatic cluster randomized controlled trial (RCT). Ethics approval was granted by the National Research Ethics Committee: North West Lancaster on March 16, 2015 (ref: 166517).

The rationale for randomizing at the cluster level was that the intervention was implemented across all eligible patients, and treatment decisions regarding individual patients remained the responsibility of HCPs at each practice [17,18].

The duration of this trial is 24 months. The installation of the prompt took place on November 1, 2015. Patients registered with control practices continued to receive usual care in line with current best practice guidelines [2].

This paper reports the trial design and baseline biomedical characteristics, including CV risk factor burden and medication management data in this study population.

Setting

Eligible practices (using EMIS Web or SystmOne IT systems and a list size of >6000 patients) within the recruitment area of Leicester City and Leicestershire County were sent an invitation summarizing the study design and protocol. Staff members who expressed an interest were offered a meeting with a member of the study team to clarify any queries regarding the study. Informed consent and information governance approval was sought among eligible practices willing to participate and documented from a senior GP partner or practice manager and Caldecott Guardian. Practices were then randomized by a member of the Leicester Clinical Trial Unit (not involved with the study) to the intervention or control arm. A 1:1 randomization was stratified based on size of diabetes register (small practices <600 patients, large practices >600 patients).

Patient Inclusion Criteria

Patient-level data were extracted for individuals aged between 17 and 76 years with a Read code for T2DM and MA or overt proteinuria on their clinical record, or individuals with T2DM and albumin-creatinine ratio (ACR)>2.5 in males and >3.5 in females on 2 consecutive occasions of >90 days and <180 days apart, having excluded a urinary tract infection [2].

Patient Exclusion Criteria

Data were not extracted if patients fulfilling the inclusion criteria were pregnant, terminally ill, or excluded from the Pay for Performance—Quality and Outcomes Framework (QOF; whole domain diabetes) [19].

Intervention

The multifactorial intervention uses an IT software prompt and care template to alert HCPs to eligible patients attending a routine consultation (Multimedia Appendices 1 and 2). The software prompt and care template was developed by an external software company, with refinement informed by feedback from HCPs during an initial focus group. The prompt and care template is triggered when patients with T2DM and MA as well as BP, TC, or HbA_{1c} above target attend a consultation. The HCP is alerted to risk factors that are above target and displays the patient's last 12-month values for each risk factor. The prompt also allows the clinician to access an evidence-based treatment algorithm recommending specific therapies that can be followed to achieve tight-targeted risk factor control (Multimedia Appendix 3). If sufficient control cannot be achieved, a link to a study email address is available for HCPs to request further individualized advice. This advice is provided within 1 week via email by a study clinician. An existing patient education leaflet emphasizing the importance of treatment adherence will also be available for eligible patients. Practice staff attended training before the prompt was installed and are provided with ongoing support and feedback during the study period (Multimedia Appendix 4).

Primary and Secondary Outcomes

The primary outcome is the proportion (%) of eligible patients meeting both of the following CV risk factor targets: BP<130/80 mm Hg and TC<3.5 mmol/L. These outcomes were selected as they are current recommended care processes and clinical outcomes of care for the management of individuals with T2DM and MA [20,2].

Secondary outcomes include the following: incidence of CV events and all-cause mortality, smoking status, glycemic control assessed by HbA_{1c}, progression in MA assessed by change in ACR, kidney function measured by change in estimated glomerular filtration rate (eGFR), changes in T2DM, BP, and cholesterol-lowering medication prescribing, including contraindications and adverse reactions. Data extracted relate to blood samples that are previously collected as part of routine care and analyzed in accordance with relevant regulations and standard operating procedures.

Sample Size Considerations

Assuming 7.5% of patients with T2DM and MA meet enhanced targets for BP (<130/80 mm Hg) and TC (<3.5 mmol/L) in the standard care group with an intraclass correlation of .05, an average of 118 patients with MA per practice (ranging from 27 to 549), data are required from 18 practices (9 in each arm) to detect an increase to 18% or higher in the proportion meeting both enhanced targets in the intervention group, with 80% power at the 5% significance level. The inflation for unequal cluster size is based on a coefficient of variation of 1.11 [21].

Data Extraction

Primary outcome is measured at baseline, 12, and 24 months post randomization in control practices and every 3 months in intervention practices to allow reporting of audit and feedback data to this group of practices.

One line per patient anonymized data is extracted using a standardized morbidity information query and export syntax (MIQUEST) query [22] in line with local governance regulations [23,24]. Time frames for data extraction are shown in Table 1. Data extraction is carried out remotely using Away from My Desk (Away From My Desk Limited, United Kingdom) [25] software. Results are uploaded to a secure online database and transferred to the research team via encrypted National Health Service email systems.

Analysis Plan

We are using a cluster randomized design with repeated measurements, and therefore, there is a high likelihood that biomedical characteristics may correlate within a cluster. We will perform linear and logistic multilevel regression analyses to study the effects of the intervention with cluster as the random effect, adjusted for the baseline value of the outcome both at practice and individual levels, using the missing indicator method for “missing” baseline data. Data will be analyzed as intention-to-treat, and differences in outcomes measures between the intervention and control groups will be calculated with 95% CI. It is also likely that not all individuals from the control group will have had regular appointments with their GP; hence, we will perform a sensitivity analysis to compare “attenders” at similar time points in the intervention versus control group.

For presentation of baseline data, we will use Pearson chi-square to analyze differences in proportions between intervention and control groups. Independent samples *t* tests will be used to analyze differences in continuous variables between study groups. Statistical analyses of the baseline data and all future analysis will be carried out using STATA version 14 [26].

Modeling the Economic Costs of the Intervention

Decision-analytic modeling will be undertaken to estimate the long-term effectiveness of the intervention compared with usual care. The costs of setting up and providing the intervention are being collected. Ongoing costs will be combined with unit costs to produce the total cost of the intervention over the 24-month study period. Unit costs for health care resources will be calculated from local and national sources and standardized to current prices. Comparisons of the primary outcome measure (individuals achieving BP and TC clinical targets) between baseline and 24-month follow-up interventions will be used to estimate the costs and incremental cost-effectiveness ratios.

The average number of eligible patients per practice will be used to estimate costs at the practice and Clinical Commissioning Group levels. All costs will be for 2016. Salary costs will be taken from Curtis (2015, [27]), and the cost of laboratory tests will be provided by the Leicester Pathology Service. Time to undertake tasks will be modeled with uncertainty in the analysis.

Results

Baseline data have been extracted from 22 practices (12 controls and 10 interventions; [Figure 1](#)) with a reference date of October 30th, 2015. The total number of patients registered at participating practices is 232,639. There are 2721 patients with T2DM meeting the study MA criteria and eligible for the study. Of these 2721, 1067 patients (39.5%; 95% CI 37.7-41.4) had a code for MA or proteinuria in their electronic medical notes.

Biomedical characteristics, current risk factor control, medical history, and current drug prescriptions of the study population are shown in [Tables 1-3](#). The mean age of patients is 62.9 (SD 10.0) years. There are no significant differences in number of male or female patients, and the study population, in keeping with local demographics, is predominantly of South Asian ethnicity (1136/1838 patients, 61.77%). The mean duration of T2DM is 10.5 (SD 7.2) years. Out of 2721 participants, 415 (15.25%) and 739 (27.16%) patients are current smokers and ex-smokers, respectively. Out of 2721 patients, 536 (19.70%) have chronic kidney disease stage 3.

The mean HbA_{1c} is 59.3 (SD 17.4) mmol/mol, mean systolic and diastolic BP (mm Hg) is 134.3 (SD 14.6) and 76.1 (SD 9.5) mm Hg, respectively, and mean TC is 4.1 (SD 0.98) mmol/L. Out of 2721 patients, 630 (23.15%) had achieved a tight BP target of <130/80 mm Hg and 707 patients (25.98%) had achieved a tight TC target of <3.5 mmol/L. Overall, 131 out of 2721 (4.81%) patients achieved all 3 “tight” CV risk factor targets. CV risk factor burden assessed by the prevalence of coronary heart disease, cerebrovascular disease, and peripheral vascular disease increased two-fold in those with eGFR<60 mL/min/1.73 m² compared with those with eGFR≥60 mL/min/1.73 m². Overall, 1076 out of 2721 (39.46%) individuals had a code for MA or proteinuria on their primary care medical record. Out of 2721 patients, 2064 (75.85%) were prescribed a nephroprotective agent, such as an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker drug, whereas 2070 patients (76.07%) were prescribed a cholesterol-lowering medication, that is, statin therapy.

Figure 1. Recruitment flowchart. T2DM: type 2 diabetes; MA: microalbuminuria.

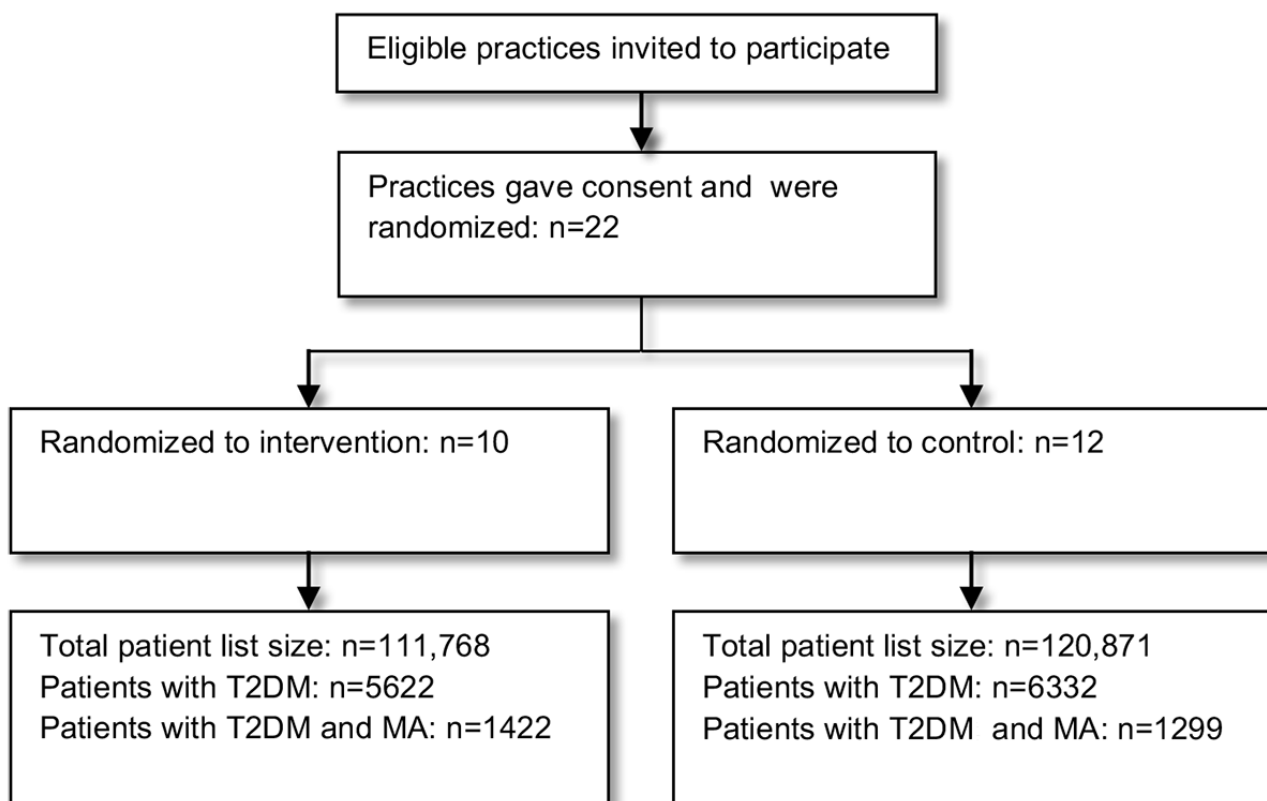


Table 1. Biomedical characteristics of eligible study patients.

Characteristics	Control (N=1299)	Intervention (N=1422)	Total (N=2721)	P value
Age in years, mean (SD)	62.8 (10.1)	62.9 (9.9)	62.9 (10.0)	.63
Age category, n (%)				
<30 years	4 (0.31)	3 (0.21)	7 (0.26)	
30-44 years	67 (5.16)	63 (4.43)	130 (4.78)	
45-65 years	623 (47.96)	712 (50.07)	1335 (49.06)	
>65 years	605 (46.57)	644 (45.29)	1249 (45.90)	
Gender, n (%)				.27
Male	776 (59.74)	820 (57.67)	1596 (58.65)	
Female	523 (40.26)	602 (42.33)	1125 (41.35)	
Ethnicity, n (%)				<.001
White	380 (38.31)	195 (23.0)	575 (31.27)	
Black	45 (4.54)	17 (2.01)	62 (3.37)	
Asian	516 (52.02)	620 (73.20)	1136 (61.77)	
Mixed	14 (1.41)	6 (0.71)	20 (1.09)	
Other	37 (3.73)	9 (1.06)	46 (2.50)	
Smoking status, n (%)				.64
Nonsmoker	750 (57.74)	817 (57.45)	1567 (57.59)	
Current smoker	205 (15.78)	210 (14.77)	415 (15.25)	
Ex-smoker	344 (26.48)	395 (27.78)	739 (27.16)	
Duration of T2DM ^a in years, mean (SD)	10.62 (7.31)	10.31 (7.14)	10.46 (7.22)	.27
HbA _{1c} ^b in mmol/mol, mean (SD)	59.8 (18.1)	58.9 (16.7)	59.3 (17.4)	.14
HbA _{1c} <53 mmol/mol, n (%)	546 (42.03)	618 (43.46)	1164 (42.78)	.45
HbA _{1c} <58.5 mmol/mol, n (%)	755 (58.12)	849 (59.70)	1604 (58.95)	.39
Total cholesterol in mmol/L, mean (SD)	4.1 (1.0)	4.1 (0.94)	4.1 (0.98)	.05
Total cholesterol<3.5 mmol/L, n (%)	335 (25.79)	372 (26.16)	707 (25.98)	.81
Total cholesterol<5 mmol/L, n (%)	1075 (82.76)	1211 (85.16)	2286 (84.01)	.07
Systolic BP ^c in mm Hg, mean (SD)	134.0 (15.0)	134.5 (14.2)	134.3 (14.6)	.82
Diastolic BP in mm Hg, mean (SD)	76.7 (9.7)	75.4 (9.2)	76.1 (9.5)	<.001
BP<130/80 mm Hg, n (%)	320 (24.63)	320 (22.50)	640 (23.52)	.19
BP<140/80 mm Hg, n (%)	608 (46.81)	670 (47.12)	1278 (46.97)	.87
eGFR ^d in mL/min, median (IQR ^e)	81.0 (62.0-90.0)	85.0 (66.0-90.0)	83.0 (64.0-90.0)	.047
CKD^f Stage 3, n (%)	260 (20.02)	276 (19.41)	536 (19.70)	.06
Stage 3a	34 (13.08)	30 (10.87)	64 (11.94)	.38
Stage 3b	22 (8.46)	13 (4.71)	35 (6.53)	.07
CKD Stage 4, n (%)	33 (2.54)	21 (1.48)	54 (1.98)	.05
CKD Stage 5, n (%)	20 (1.54)	13 (0.91)	33 (1.21)	.14
Medical history, n (%)				
Myocardial infarction	97 (7.47)	89 (6.26)	186 (6.84)	.21
Acute coronary syndrome	51 (3.93)	57 (4.01)	108 (3.97)	.91
Angina	120 (9.24)	132 (9.28)	252 (9.26)	.97
Ischemic heart disease	249 (19.17)	264 (18.57)	513 (18.85)	.68

Characteristics	Control (N=1299)	Intervention (N=1422)	Total (N=2721)	P value
Transient ischemic attack	66 (5.08)	35 (2.46)	101 (3.71)	<.001
Stroke	46 (3.54)	55 (3.87)	101 (3.71)	.65
Peripheral vascular disease	48 (3.70)	34 (2.39)	82 (3.01)	.047
Revascularization procedure	92 (7.08)	40 (2.81)	132 (4.85)	<.001
Bypass graft	47 (3.62)	53 (3.73)	100 (3.68)	.88
Number of study risk factors controlled, n (%)^g				.21
0	336 (25.87)	337 (23.70)	673 (24.73)	
1	579 (44.57)	680 (47.82)	1259 (46.27)	
2	309 (23.79)	336 (23.63)	645 (23.70)	
3	70 (5.39)	61 (4.29)	131 (4.81)	
MA ^h /proteinuria code, n (%)	410 (31.56)	666 (46.84)	1076 (39.54)	<.001

^aT2DM: type 2 diabetes.

^bHbA_{1c}: glycated hemoglobin.

^cBP: blood pressure.

^deGFR: estimated glomerular filtration rate.

^eIQR: interquartile range.

^fCKD: chronic kidney disease.

^gHbA_{1c} <7.5% (58.5 mmol/mol), total cholesterol <3.5 mmol/L, BP <130/80 mm Hg.

^hMA: microalbuminuria.

Table 2. Vascular burden between patient groups categorized by chronic kidney disease stages.

Disease characteristic	Patients with MA ^a and eGFR ^b <60			Patients with MA and eGFR >60		
	Control (N=280)	Intervention (N=258)	Total (N=538)	Control (N=1019)	Intervention (N=1164)	Total (N=2183)
Cardiovascular disease, n (%)						
Myocardial infarction	33 (11.8)	29 (11.2)	62 (11.5)	63 (6.18)	58 (4.98)	121 (5.54)
Acute coronary syndrome	19 (6.8)	16 (6.2)	35 (6.5)	32 (3.14)	41 (3.52)	73 (3.34)
Angina	38 (13.6)	30 (11.6)	68 (12.6)	81 (7.95)	101 (8.68)	182 (8.34)
Ischemic heart disease	78 (27.9)	75 (29.1)	153 (28.4)	169 (16.58)	186 (15.98)	355 (16.26)
Coronary artery bypass graft	18 (6.4)	16 (6.2)	34 (6.3)	29 (2.58)	36 (3.09)	65 (2.98)
Cerebrovascular disease, n (%)						
Transient ischemic attack	19 (6.8)	10 (3.9)	29 (5.4)	47 (4.61)	25 (2.15)	72 (3.30)
Stroke	15 (5.4)	16 (6.2)	31 (5.8)	30 (2.94)	38 (3.26)	68 (3.11)
Peripheral vascular disease	21 (7.5)	16 (6.2)	37 (6.9)	27 (2.65)	18 (1.55)	45 (2.06)
Hypertension (BP ^c >130/80)	80 (28.6)	81 (31.4)	161 (29.9)	236 (23.16)	235 (20.19)	471 (21.58)
Hyperlipidemia (TC ^d >4.0)	125 (44.6)	110 (42.6)	235 (43.7)	482 (47.30)	504 (43.30)	986 (45.17)

^aMA: microalbuminuria.

^beGFR: estimated glomerular filtration rate.

^cBP: blood pressure.

^dTC: total cholesterol.

Table 3. Drug prescribing in eligible study individuals at baseline.

Drug	Control (N=1299), n (%)	Intervention (N=1422), n (%)	Total (N=2721), n (%)	P value
Long-acting insulin	225 (17.32)	268 (18.85)	493 (18.12)	.30
Short-acting insulin	92 (7.08)	123 (8.65)	215 (7.90)	.13
Metformin	926 (71.29)	971 (68.28)	1897 (69.72)	.09
Sulphonylurea	422 (32.49)	434 (30.52)	856 (31.46)	.27
Dipeptidyl peptidase-4 (DPP-4)	205 (15.78)	228 (16.03)	433 (15.91)	.86
Thiazolidinediones (TZD)	78 (6.00)	28 (1.97)	106 (3.90)	<.001
Glucagon-like peptide-1 receptor antagonist (GLP-1 RA)	56 (4.31)	39 (2.74)	95 (3.49)	.03
Sodium glucose transporter-1 inhibitor (SGLT-2i)	28 (2.16)	20 (1.41)	48 (1.76)	.14
Meglitinide	220 (16.94)	311 (21.87)	531 (19.51)	.001
Calcium channel blocker (CCB)	524 (40.34)	592 (41.63)	1116 (41.01)	.49
Diuretic	388 (29.87)	412 (28.97)	800 (29.40)	.61
Angiotensin-converting enzyme (ACE) inhibitor	666 (51.27)	713 (50.14)	1379 (50.68)	.56
Angiotensin receptor blocker (ARB)	349 (26.87)	336 (23.63)	685 (25.17)	.05
Beta blocker	376 (29.95)	407 (28.62)	783 (28.78)	.85
Alpha blocker	393 (30.25)	455 (32.00)	848 (31.17)	.23
Aspirin	393 (30.25)	455 (32.00)	848 (31.17)	.33
Clopidogrel	74 (5.70)	76 (5.34)	150 (5.51)	.69
Statin	959 (73.83)	1111 (78.13)	2070 (76.07)	.01
Fibrate	29 (2.23)	32 (2.25)	61 (2.24)	.98
Ezetimibe	26 (2.00)	37 (2.60)	63 (2.32)	.30
Warfarin	66 (5.08)	79 (5.56)	145 (5.33)	.58

Discussion

Overview

This paper describes the design and baseline characteristics of a pragmatic cluster RCT that will investigate the effectiveness of a multifactorial intervention. The study's achievements thus far include the following: establishing the infrastructure for the trial, recruitment of the required number of GP practices, provision of training for HCPs at intervention practices, and baseline data extraction. Analysis of the baseline data shows poor coding levels of individuals meeting the diagnostic criteria for MA within their medical record. Subgroup analysis by eGFR highlights the increased vascular burden in patients with kidney disease.

Principal Findings

MA is an easily available integrated marker, suggesting subclinical generalized involvement of the vascular system, predisposing individuals with T2DM to increased risk of CV disease. Evaluation of abnormal urinary albumin excretion through urinary ACR in individuals with T2DM is a specific and cost-effective method to help identify individuals who can benefit from additional intensive, targeted interventions involving tight CV risk factor control [3,28]. However, despite the plethora of evidence, UK National Audit data from 2015 to 2016 showed that only 40.2% people with T2DM were reaching

all 3 treatment targets [29] ($HbA_{1c} < 58$ mmol/mol, $BP < 140/80$ mm Hg, and $TC < 5$ mmol/L). Although we used tighter risk factor targets in our study, which may not conform to targets set out by practicing clinicians in primary care (eg, UK QOF targets), it can be argued that the nature of a high-risk state such as T2DM with MA deserves stricter cardio-metabolic control to achieve greater CV mortality and morbidity benefits [3,28,30]. However, individualization of therapy must take precedence as emphasized in the National Institute For Health and Care Excellence (NICE) guidelines for T2DM in the United Kingdom [2] and in the new 2017 American Diabetes Association statement on standards of medical care in diabetes [31], which encourages clinicians to use a pragmatic approach and be cognizant of the "risk-benefits" while using treatments to minimize CV risk. Accordingly, although our baseline data in this high-risk population suggest "adequate to satisfactory" performance in achieving tight cardio-metabolic risk factors targets, prescribing patterns particularly relating to nephroprotective agents and statin therapy and achieving all "prescribed" care processes such as "coding for MA" could be improved.

A number of reasons may explain why a high proportion of individuals do not achieve cardio-metabolic targets in primary care, including clinical inertia, aiming only for "prescribed" QOF targets [32,33], lack of time for treating complex patients,

gaps in clinician knowledge, and the need for a well-organized health care system to manage chronic conditions [34]. However, improvements in clinical care processes and targeted control of CV risk factors in high-risk individuals with T2DM and MA have recognized benefits and should be pursued without delay and with commitment, both from the perspective of the HCP and the affected individual [3,30]. Our hypothesis was that a multifaceted, multifactorial intervention including the use of an electronic “Prompt” readily available and visible to the treating HCP during “limited” consultation times would serve as an “aide-memoire” to intensify treatment targets and improve clinical outcomes.

A cluster randomized design was chosen to avoid contamination [35] which may have occurred if it was at the patient level. Furthermore, HCPs could face conflict if they were to deliver a purposeful intensive intervention only to certain individuals within their population.

The GP prompt study, to our knowledge, is the largest RCT assessing the effectiveness of a practice-level intervention to support management of a multiethnic population diagnosed with T2DM and MA. Baseline data give contemporary estimates for adherence to best practice risk factor targets and the increased vascular burden in these affected individuals.

Limitations

An identified weakness of this trial may relate to the chosen method of data collection. To allow collection of large amounts of data and cluster randomization at the practice level, Read-coded primary care data are being collected using MIQUEST. The accuracy of the data and their usefulness as resource for study are therefore dependent on the coding practices of individual clinicians in individual practices. For example, level of coding within primary care for ethnicity has previously been found to be poor [36]. Our baseline data suggest that although recording of ethnicity data has improved, there remains significant variation between practices. This lack of complete data may limit our ability to perform secondary subgroup analysis to study interracial variations [37].

Anecdotal evidence suggests that coding quality for MA within primary care data is poor. Putative factors may include requirement for more than one sample to make a diagnosis, which may cause delays in diagnosis; infrequent testing and recall; and lack of recognition of MA as an important “CV risk marker.” Furthermore, it is likely that recommended processes of care that are performed frequently (BP, HbA_{1c}, and lipid checks) may be more diligently recorded than those recommended and/or performed less frequently (eg, MA, foot examination). To account for this, we used pragmatic inclusion criteria based on international guidelines for MA [2]. We used a definition of 2 abnormal ACR values (2.5 mg/mmol for men, >3.5 mg/mmol for women) >90 days but <180 days apart [38]. Using this definition, only 1076 out of 2721 patients (39.54%) with 2 abnormal ACR values (>2.5 in males and >3.5 females) on 2 occasions >90 days and <180 days apart were coded as having MA or overt proteinuria. We were not able to exclude patients with proteinuria or urinary tract infection as per national guidance because of the methodology by which such data are coded. Despite this, prevalence rates for MA within the study population are broadly in line with other large contemporary population-based studies [39].

Conclusions

Multifactorial-targeted interventions in individuals with T2DM and MA have shown efficacy in reducing CV events and mortality, mostly in specialist settings. However, their effectiveness, implementation, and cost-effectiveness in a primary care setting have not been adequately tested. The results of this study, including a comprehensive cost-effectiveness analysis, will inform on these issues and will be published in 2018. If the results of the GP prompt study are positive, there is a potential for “scaling up” under real-world conditions to reach a greater proportion of the eligible population. Skills, competencies, and workforce required for wider implementation would need to be assessed, and the results of this study would provide policy makers and senior decision makers with vital information to facilitate widespread adoption into CV risk reduction programs.

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Conflicts of Interest

MJD has acted as a consultant, advisory board member, and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen; an advisory board member for Servier; and as a speaker for Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, and Janssen. KK has been a consultant, speaker, and advisory board member for Amgen, AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Merck Sharp and Dohme, Janssen, and Boehringer Ingelheim. He has also received grants in support of investigator-initiated trials from AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, Merck Sharp and Dohme, and Roche. WC has received speaker fees, education and grants from Sanofi-Aventis, Novo Nordisk, Boehringer Ingelheim, Lilly, and Internis Pharmaceuticals limited. AW, LG, HD, WG, and GG have no conflicts of interests to declare.

Multimedia Appendix 1

Clinical system "prompts."

[[PDF File \(Adobe PDF File\), 1MB](#) - [resprot_v7i6e152_app1.pdf](#)]

Multimedia Appendix 2

Enhanced care template.

[[PDF File \(Adobe PDF File\), 68KB](#) - [resprot_v7i6e152_app2.pdf](#)]

Multimedia Appendix 3

Treatment algorithm.

[[PDF File \(Adobe PDF File\), 190KB](#) - [resprot_v7i6e152_app3.pdf](#)]

Multimedia Appendix 4

HCP training programme.

[[PDF File \(Adobe PDF File\), 15KB](#) - [resprot_v7i6e152_app4.pdf](#)]

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Abbreviations

ACR: albumin-creatinine ratio
BP: blood pressure
CKD: chronic kidney disease
eGFR: estimated glomerular filtration rate
GP: general practitioner
HbA_{1c}: glycated hemoglobin
HCP: health care professional
IQR: interquartile range
IT: information technology
MA: Microalbuminuria
MIQUEST: morbidity information query and export syntax
QOF: Quality and Outcomes Framework
RCT: randomized controlled trial
TC: total cholesterol
T2DM: type 2 diabetes

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Protocol

Mobile Phone Cognitive Bias Modification Research Platform for Substance Use Disorders: Protocol for a Feasibility Study

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Abstract

Background: Cognitive biases refer to automatic attentional and interpretational tendencies, which could be retained by cognitive bias modification interventions. Cristea et al and Jones et al have published reviews (in 2016 and 2017 respectively) on the effectiveness of such interventions. The advancement of technologies such as electronic health (eHealth) and mobile health (mHealth) has led to them being harnessed for the delivery of cognitive bias modification. To date, at least eight studies have demonstrated the feasibility of mobile technologies for the delivery of cognitive bias modification. Most of the studies are limited to a description of the conventional cognitive bias modification methodology that has been adopted. None of the studies shared the developmental process for the methodology involved, such that future studies could adopt it in the cost-effective replication of such interventions.

Objective: It is important to have a common platform that could facilitate the design and customization of cognitive bias modification interventions for a variety of psychiatric and addictive disorders. It is the aim of the current research protocol to describe the design of a research platform that allows for customization of cognitive bias modification interventions for addictive disorders.

Methods: A multidisciplinary team of 2 addiction psychiatrists, a psychologist with expertise in cognitive bias modification, and a computer engineer, were involved in the development of the intervention. The proposed platform would comprise of a mobile phone version of the cognitive bias task which is controlled by a server that could customize the algorithm for the tasks and collate the reaction-time data in realtime. The server would also allow the researcher to program the specific set of images that will be present in the task. The mobile phone app would synchronize with the backend server in real-time. An open-sourced cross-platform gaming software from React Native was used in the current development.

Results: Multimedia Appendix 1 contains a video demonstrating the operation of the app, as well as a sample dataset of the reaction times (used for the computation of attentional biases) captured by the app.

Conclusions: The current design can be utilized for cognitive bias modification across a spectrum of disorders and is not limited to one disorder. It will be of value for future research to utilize the above platform and compare the efficacy of mHealth approaches, such as the one described in this study, with conventional Web-based approaches in the delivery of attentional bias modification interventions.

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KEYWORDS

attention bias modification; eHealth; mHealth; development

Introduction

Cognitive biases include automatic attentional and interpretational tendencies [1]. Attentional biases, which refer to the preferential tendency for attention to be allocated towards or away from stimuli that are emotionally salient for the individual, have been found to be present in a variety of disorders, ranging from depression and anxiety disorders to addictive disorders [2]. These automatic processes would result in individuals with an anxiety disorder to attend to threat related cues, individuals with depression to attend to negative information, and individuals with addictive disorders to attend to substance-related cues. As such, cognitive biases are highly prevalent and have been implicated in the psychopathologies of various disorders [3-5].

Various theoretical approaches have helped to account for the role of these automatic processes in the different psychopathologies, but, perhaps the best developed theoretical model to date, is the dual-process model for addictive disorders [6]. The dual-process theoretical model proposes that with the recurrent use of a substance, this facilitates increased automatic processing of substance-related cues, with a resultant inhibition of the normal cognitive control processes [6]. Along with the increased recognition of cognitive biases, there has been further research examining how these biases could be modified. Several different cognitive bias modification approaches are routinely used, namely that of the attention bias modification, cognitive bias modification for interpretations, spatial cueing tasks, and attentional visual search [7]. To date, there have been a number of studies reported that have investigated the effectiveness of bias modification. In 2016, Cristea et al conducted a meta-analysis of participants with either a tobacco or alcohol addiction and considered the effect size of cognitive bias modification on cognitive biases and on addiction-related outcomes, such as cravings [8]. This study reported that bias modification had a significant effect on cognitive bias, with an effect size of 0.60 (calculated using Hedge *g*). Despite its effect on cognitive biases, there were no effects reported on other addiction outcomes. In a commentary published online, responding to the study by Cristea et al [8], a key limitation of the meta-analysis was identified, namely that Cristea et al considered clinical and nonclinical trials jointly in their synthesis of the results. When considering only clinical trials, there was a significant effect of bias modification. This finding from the meta-analysis demonstrates the importance of targeting automatic processes and the potential efficacy of bias modification in substance using individuals. A review of meta-analyses published by Jones et al in 2017 [1], conducted for a diverse group of participants, reported that the current evidence supports the effectiveness of bias modification, mainly for anxiety disorders.

Conventional cognitive bias interventions have typically been delivered using a computer in the confines of a laboratory, but there is potential to change this. In the past decade, there have been an increasing number of remote online therapies available and this has been attributed to the advances in eHealth, or electronic health. eHealth technologies facilitate the delivery of online psychotherapy at a low cost and allows therapy to be

highly accessible and anonymous [9]. There have been an increasing number of studies examining the effectiveness of Web-based cognitive bias modification interventions. In 2015, Wittekind et al evaluated an online avoidance retraining intervention for 257 individuals with a tobacco use disorder; and demonstrated that avoidance bias retraining was associated with a significant reduction in the number of cigarettes smoked and the cravings to smoke [10]. In 2017, Cogle et al conducted a trial which evaluated an online interpretation bias modification program for hostility with 58 individuals [11]. They found that the online intervention led to a greater reduction in interpretative bias compared to the control group. These trials have demonstrated the feasibility and effectiveness of Web-based bias modifications. Further advancement in technology, coupled with increased ownership of mobile devices, has led to there being increasingly more interventions that use mobile technologies (mHealth). Based on the published literature to date, there are several studies that have evaluated the potential and effectiveness of mHealth bias modification. Of the studies, seven reported that mHealth bias modification was effective for participants with a variety of disorders, namely insomnia, alcohol, tobacco use, or social anxiety disorders [12-18]. mHealth technologies are increasingly being harnessed for the delivery of bias modification, as mobile technologies allow for the training to be conducted in diverse locations, thus helping in the generalization of clinical benefits [19]. In addition, such technologies help to increase accessibility to the intervention and aid in the reduction of costs associated with treatment. The use of mobile technologies in the delivery of bias modification interventions could help to improve outcomes, in that it helps to increase the frequency of training [19]. mHealth technologies have an advantage over existing Web-based versions, given that web interventions would require individuals to be consistently connected to the internet to undertake the bias modification task. There is also the potential to couple the bias modification with other sensors in the mobile phone, such that users will be prompted to engage in training tasks to help them with their symptoms if they are deemed to be in a high-risk locality [20].

While the existing mHealth studies have demonstrated the feasibility of such technologies, most of these studies are limited to a description of the conventional bias modification methodology that has been adopted. None of the previous studies have shared the platform that they have used in the development of their cognitive bias task, thus limiting the replicability of the intervention. Most studies are limited to a description of the conventional task paradigm that have been adopted, for example, in the study reported by Clarke et al in 2016, it was reported that their intervention task was based on the conventional attentional probe training paradigm [12]. In the supplementary material, details of the words that were utilized for their task were provided. Whilst this allows for replicability to a certain extent, a number of resources are needed to develop a mobile version of the platform to deliver cognitive bias modification. Hence, it is thus of great import to have a common platform that could easily facilitate the design and customization of such interventions for a variety of psychiatric disorders. As a start, we will describe the design of a research platform that allows the customization of bias modification interventions for a range of substance use disorders.

Methods

Overview of Research Platform

A multidisciplinary team, comprising of 2 psychiatrists specializing in addiction psychiatry, a psychologist with prior expertise on attentional bias modification, and a computer engineer were involved in the development of the research platform. It was decided that the platform would comprise of a mobile phone version of the cognitive bias task (as an example, the visual probe task), which is controlled both by a server that could customize the algorithm for the tasks and collate the reaction time data in realtime (Figure 1). The server would also allow the researcher to program the specific set of images that will be present in the task. The mobile phone app would synchronize with the backend server in realtime.

The mobile phone app that will be created needs to be modelled against the conventional visual probe task approach [21]. Based on the conventional approach, in the assessment phase, individuals would be presented with a fixation cross upon commencement. After that, both a neutral and non-neutral stimulus would be presented simultaneously. Both of these stimuli would disappear and a probe (usually in the form of an asterisk) would replace either stimulus. Individuals are required to indicate the position of the asterisk by indicating a response within a predetermined time. In the bias assessment phase, the asterisk would replace either stimulus equally (50% of the time). However, in the bias modification phase, the asterisk would replace the neutral stimulus all the time (100% of the time). Individuals with biases would spend more time engaging with the stimuli and have difficulties with disengaging after. This will be reflected in their increased reaction time towards identifying the exact locality of the probe (asterisk).

The graphic user interface will be similar across the different substance disorders. The server will allow for the collation of reaction time data, as well as other variables that are essential when using reaction time to compute the presence of attentional biases. These variables include the positions of the probes, the positions of the substance-related stimuli, and whether the participant has indicated a correct response. Figure 2 provides an overview of the sample dataset that is collated by the server. In addition, the server has been programmed with a specific algorithm, such that it enables the control of the frequencies of the probe replacing the substance stimuli (whether 50% or 100%). The research platform would also allow the researchers to vary the number of repeats of a particular set of images. Figure 3 provides an overview of how the server is able to control these parameters.

Development of Research Platform

The cognitive bias modification app was developed using an open-source cross-platform gaming software, React Native. The development team decided to utilize this approach for several reasons. The integration of an open-source approach would ensure that the intervention is compatible and could be utilized across a variety of platforms, without any differences between platforms. Thus, participants are able to undertake the task on their mobile phone devices, as well as on a normal computer. The gaming platform that has been used also allows for the future incorporation of gamification elements, as gamification has been shown to help increase motivation for bias modification [22]. In addition, the current platform is versatile and allows for scaling or modification of the entire program to be used for a different disorder. This would drastically reduce the time and cost associated with development, while ensuring that the timings of the conventional paradigms are retained.

Figure 1. Overview of the research platform for the cognitive bias intervention for substance use disorders.

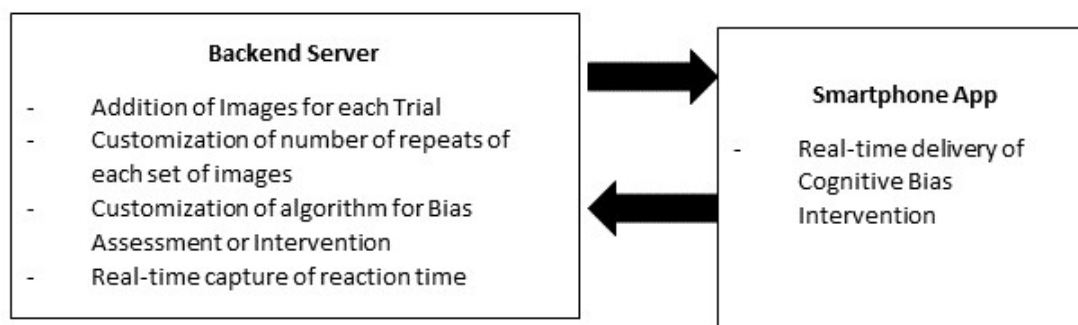




Figure 2. Sample dataset of reaction time data collated by the server.

Results Sobriety Admin 

Filter EXPORT 











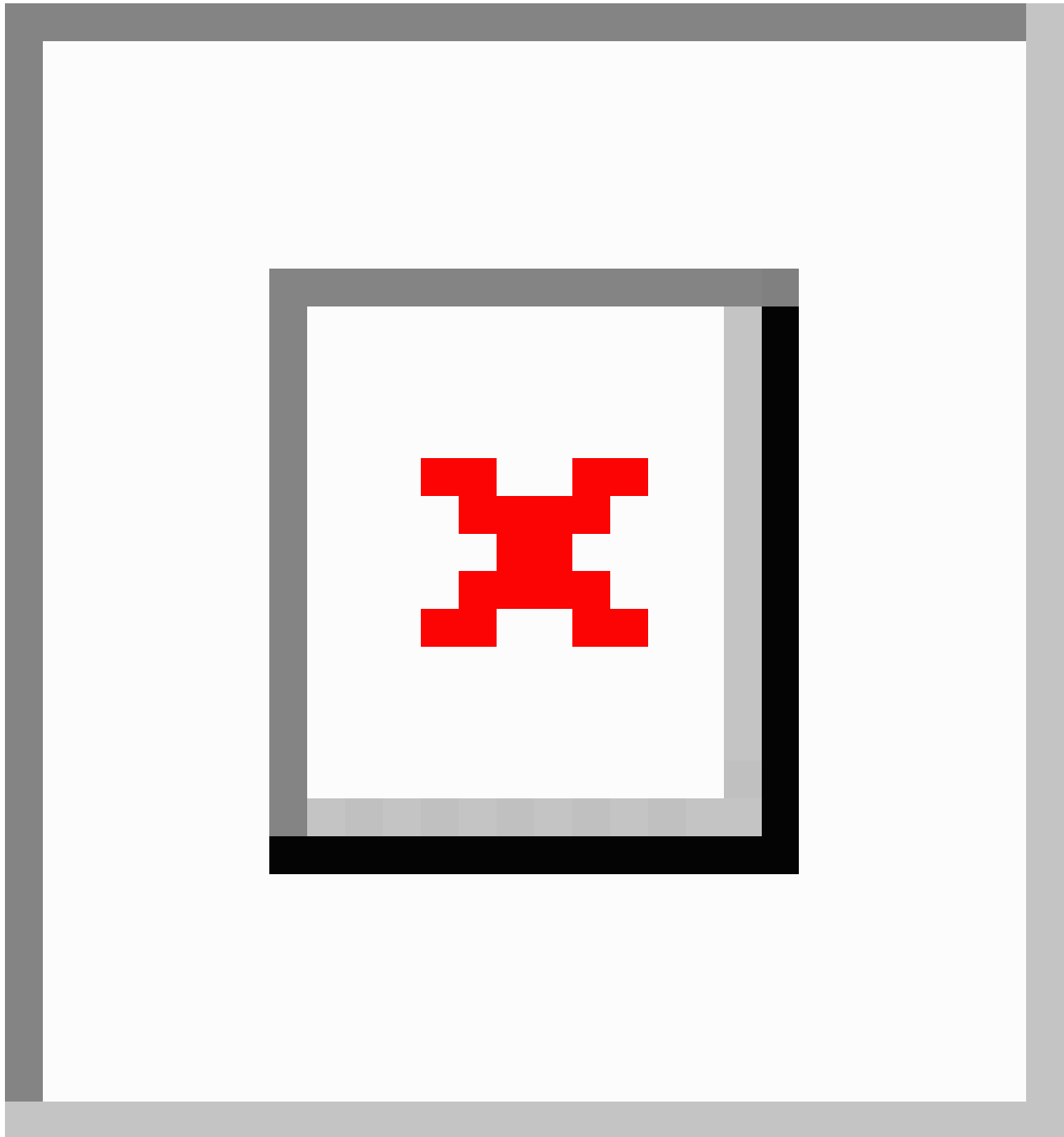
Created Date	Name	Type	Category	Image	Asterisk	Test Result	Time (ms)
Dec 12, 2017 11:08:06	 Melvyn	Assessment	Alcohol	Left	Right	incorrect	2,000
Dec 12, 2017 11:08:03	 Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:08:00	 Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:57	 Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:07:54	 Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:50	 Melvyn	Assessment	Alcohol	Right	Left	incorrect	2,000
Dec 12, 2017 11:07:47	 Melvyn	Assessment	Alcohol	Right	Right	incorrect	2,000
Dec 12, 2017 11:07:44	 Melvyn	Assessment	Alcohol	Left	Left	incorrect	2,000
Dec 12, 2017 11:07:41	 Melvyn	Assessment	Alcohol	Left	Right	incorrect	2,000
Dec 12, 2017 11:07:38	 Melvyn	Assessment	Alcohol	Left	Left	correct	1,929

Figure 3. Ability of the server to customize the algorithm for the Visual Probe task.



Results

[Multimedia Appendix 1](#) contains a video demonstrating the operation of the app, as well as a sample dataset of the reaction times captured by the app ([Multimedia Appendix 2](#)).

Discussion

Principal Findings

The current design could be utilized for cognitive bias modification across a spectrum of disorders and is not limited to just one disorder. This research platform could be adopted by various cognitive bias modification interventions and the usage of this platform would potentially drive down the costs

associated with the development of such mHealth interventions. This is congruent with the recommendation made in the study published by Zhang et al for the usage of low-cost methodologies in app development [23]. The framework we have developed could be easily distributed and fellow researchers could make use of the created platform for their own interventions. While we have presented and discussed evidence mainly for substance use disorder, cognitive bias modification is also efficacious for other disorders, such as social anxiety disorders [24]. As compared to the conventional method, or even Web-based interventions, the mobile phone bias modification intervention would imply that individual users are no longer confined to a laboratory environment to receive the intervention. Individuals can make use of the interventions

in their naturalistic environments, and the app could also be coupled with geolocation services intrinsic to the mobile phone. By doing so, this would facilitate the delivery of timely interventions when individuals are in their high-risk locality, when they are most prone to a relapse.

Furthermore, there has been growing interest in consideration of incorporating of serious game elements to conventional cognitive bias tasks [7], and subsequently a study has been published which highlighted several possible gamification strategies [22]. A variety of serious games strategies have been proposed, which include the addition of game elements, the intrinsic integration with the evidence-based task as a basis, intrinsic integration leaving the evidence base task intact, or the addition of a game shell around the original evidence base task [22]. These four different mechanisms could easily be achievable in the current design, given that the design of the current mobile phone based attentional bias modification paradigm has been based on a gaming engine. Whilst most gamification techniques

seek to increase an individual's motivation to continue with a task, it is important to recognize that the consequences of the game do have an impact on gaming behaviors [19]. In our case, the pairing of an aversive consequences in the game play might help to enhance our aim of decreasing individuals' typical behavior towards rewarding stimuli.

Conclusions

In conclusion, we have shared a research platform for the design of a mobile phone version of a bias modification task, which could be easily modified to be applied to a spectrum of disorders. It will be of value for future research to utilize the above platform and compare the efficacy of mHealth approaches, such as the one described in this study, with conventional Web-based approaches in the delivery of cognitive bias modification interventions. Additionally, the use of a gaming platform in the current design opens future opportunities to consider the addition of serious gaming elements to enhance the appeal of these tasks.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Demonstration of the research platform app.

[[MP4 File \(MP4 Video\), 15MB - resprot_v7i6e153_app1.mp4](#)]

Multimedia Appendix 2

Sample dataset of reaction times.

[[XLSX File \(Microsoft Excel File\), 16KB - resprot_v7i6e153_app2.xlsx](#)]

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Abbreviations

eHealth: electronic health

mHealth: mobile health

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Protocol

Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians: Protocol for a Prevalence Study of Oral-Related Human Papillomavirus and Cost-Effectiveness of Prevention

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Abstract

Background: Oropharyngeal cancer is an important, understudied cancer affecting Aboriginal and Torres Strait Islander Australians. The human papillomavirus (HPV) is a significant risk factor for oropharyngeal cancer. Current generation HPV vaccines are effective against the 2 most common types of high-risk HPVs in cancer (hrHPVs 16/18).

Objectives: This study aims (1) to yield population estimates of oncogenic genotypes of HPV in the mouth and oropharynx of defined Aboriginal and Torres Strait Islander populations; (2) to estimate the proportion of oropharyngeal cancer attributable to HPV among these Australian citizens; (3) to estimate the impact of HPV vaccination as currently implemented on rates of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians; and (4) taking into account impact on oropharyngeal as well as cervical cancer, to evaluate efficacy and cost-effectiveness of targeted extended HPV vaccination to older ages, among our study population.

Methods: Our study design and operation is straightforward, with minimal impost on participants. It involves testing for carriage of hrHPV in the mouth and oropharynx among 1000 Aboriginal South Australians by simple saliva collection and with follow-up at 12 and 24 months, collection of sexual history at baseline, collection of information for estimating health state (quality-of-life)

utilities at baseline, genotyping of viruses, predictive outcome and cost-effectiveness modeling, data interpretation and development of vaccination, and follow-up management strategies driven by the Aboriginal community.

Results: Participant recruitment for this study commenced in February 2018 and enrollment is ongoing. The first results are expected to be submitted for publication in 2019.

Conclusions: The project will have a number of important outcomes. Synthesis of evidence will enable generation of estimates of the burden of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians and indicate the likely effectiveness and cost-effectiveness of prevention. This will be important for health services planning, and for Aboriginal health worker and patient education. The results will also point to important areas where research efforts should be focused to improve outcomes in Aboriginal and Torres Strait Islander Australians with oropharyngeal cancer. There will be a strong focus on community engagement and accounting for the preferences of individuals and the community in control of HPV-related cancers. The project has international relevance in that it will be the first to systematically evaluate prevention of both cervical and oropharyngeal cancer in a high-risk Indigenous population taking into account all population, testing, and surveillance options.

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Papillomaviridae; oropharyngeal neoplasms; vaccination; population

Introduction

Human Papilloma Viruses

Human papillomaviruses (HPVs) are a heterogeneous group of over 100 genotypes, being circular, double-stranded DNA viruses that grow in stratified epithelia of skin and mucous membranes. There are approximately 15 HPV types that have potential to cause cancer. Before implementation of vaccination, a restricted number of these genotypes, known as high risk or oncogenic types, were the most common sexually transmitted infection in Australia, with an estimated 4 out of 5 Australians having a high-risk HPV (hrHPV) infection at some point in their lives [1]. The most common hrHPV types are HPV-16 and HPV-18. These HPVs are a precursor to a range of cancers in both females and males (particularly cervical cancer, other anogenital cancers and oropharyngeal cancer) and are usually acquired within 2-5 years of commencing sexual activity [2]. Preventing such HPV infections is a public health priority to reduce cancer and HPV-associated complications [3].

The rate of carriage of hrHPV at a population level at sites relevant to cancer (anogenital and oropharyngeal) in Australia is difficult to characterize; most surveys have not been national or representative, and almost all have focused on females only. Although there are some general population oral HPV DNA prevalence data [4], the big gap in the knowledge base is the oral and oropharyngeal HPV prevalence in a high-risk group for oropharyngeal cancers, Aboriginal and Torres Strait Islander Australians [5].

Human Papillomavirus and Cervical Cancers

Cervical cancer is the fourth most common cancer of women internationally [6]. Virtually, all cervical cancers are attributable to infection with oncogenic genotypes of HPV [7]. In an international study, incidence of cervical cancer was found to be higher among Indigenous women than among non-Indigenous women in most countries (Australia, New Zealand, Canada, and the United States) [8]. In Australia, there are undisputedly

higher rates of cervical cancer and mortality among Indigenous compared with non-Indigenous women [9].

Human Papillomavirus and Oropharyngeal Cancers

Oropharyngeal cancers include cancer of the middle part of the throat: the tonsils, posterior one-third of the tongue, and lateral and posterior walls of the oropharynx [10]. Approximately 90% of oropharyngeal cancers are squamous cell carcinomas [11]. Tobacco and heavy alcohol use, often in a background of diets poor in essential antioxidant vitamins and minerals, are major risk factors [12]. The impact of tobacco and alcohol is synergistic, ie, a person exposed to both has multiplicative, not just additive, risk [13]. Additional risk indicators include being male, older age, having infection with *Candida* or a pro-inflammatory bacteriale, or a compromised immune system [14,15]. Survival from oropharyngeal cancers is comparatively low. This is because they are frequently asymptomatic and diagnosed at a late stage. In general, more than half of all persons with oropharyngeal cancer have regional or distant metastases at diagnosis [16]. Once the cancer has metastasized, prognosis is worse than when localized. Relative 5-year survival in the United States is 82% for localized disease, 56% for regional lymph node spread, and 33% for distant metastases [17].

In addition to tobacco and alcohol, HPV has been increasingly identified as a significant risk factor for oropharyngeal cancer [18]. Both oral HPV prevalence and HPV-positive oropharyngeal cancers are associated with younger age (compared with tobacco and alcohol-related oropharyngeal cancer), sex (higher incidence in males), sexual behaviors (higher among those who have ever had oral sex), and number of sexual partners (applies particularly to men, but works both ways) [19]. These factors increase the risk of cancer development 3- to 5-fold [20]. The proportion of oropharyngeal cancers that are HPV-positive has increased over the last decade in Europe and North America to an estimated 70% [21]. Indicative data from Australia suggest a similar increase in the fraction of oropharyngeal cancers that might be attributable to HPV [22].

Burden of Oropharyngeal Cancer in Australia

Head and neck cancers (of which oropharyngeal cancer is one) have been described as being more emotionally traumatic than any other form of cancer [23,24]. Treatments can be debilitating and disfiguring, with patients frequently going on to live with chronic functional impairment in a range of areas including speech and swallowing [25]. There are substantial effects on oral health and nutrition [26], on social functioning, and on mood, with an often immediate decrease in health-related quality of life which persists long term [24]. Ariyawardana and Johnson reported that, although rates of overall lip, oral cavity, and oropharyngeal cancer declined between 1982 and 2008, presumably due to decreased alcohol and tobacco use, and potentially improved sun protection for lip cancer, they were still high [11]. When considered in isolation, rates of oropharyngeal cancer increased during this time (1.2% per annum for men, 0.8% per annum for females), possibly due to an increased incidence of HPV-related oropharyngeal cancer [11]. Hong reported that the proportion of oropharyngeal cancers which were positive for HPV DNA and p16 increased from 20.2% in 1987-1995 to 63.5% in 2006-2010 [27].

Oropharyngeal Cancer in Aboriginal and Torres Strait Islander Australians

There is little documented evidence on the incidence of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians at a national level. Johnson and colleagues reported that Indigenous persons living in Queensland (who comprise 4% of the Queensland population) were more likely than the total Queensland population to be diagnosed with certain head and neck cancers between 1997 and 2012, specifically base of tongue or tonsil or oropharynx (standardized incidence ratio=2.16; n=81) [5]. Five-year cause-specific survival estimates, adjusted for age and sex, were 75% (95% CI 74-76%) for non-Indigenous persons and 43% (95% CI 38-49%) for Indigenous persons. Similar differentials in survival were observed for cancers of the base of tongue/tonsil/oropharynx (64% vs 27%) and mouth/oral cavity (66% vs 42%) [28]. In 2003, the rate ratio of disability-adjusted life years due to oral cavity and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians was 3.8 times that reported for the total Australian population [29].

Oropharyngeal Cancer Risk Factors Among Indigenous Australians

As with the general population, alcohol and tobacco use are often cited to be significant risk factors for oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians, although the population attributable fraction for HPV-related oropharyngeal cancers in this group is unknown [9]. Aboriginal and Torres Strait Islander Australians generally commence tobacco smoking at an earlier age, continue to smoke for longer, and make fewer quitting attempts than non-Indigenous Australians [30]. In 2012-2013, Aboriginal and Torres Strait Islander Australians were 2.6 times more likely than non-Indigenous Australians to be current daily smokers (40% compared with 15% after age standardization) [31].

High-Risk Human Papillomavirus Among Aboriginal and Torres Strait Islander Australians

There are currently no population estimates of carriage of hrHPV in the upper aero-digestive tract among Aboriginal and Torres Strait Islander Australians. This is a substantial deficit in the contemporary knowledge base, particularly given the higher risk for oropharyngeal cancer among this population. To determine prevalence of hrHPV, and risk factors associated with the infection among this population, data on prevalence using sensitive HPV detection methods are necessary.

Efficacy of Human Papillomavirus Vaccination

Prevention of acquiring a persistent infection with a hrHPV through vaccination is a cost-effective and life-saving intervention to decrease the burden of HPV-related cancers in Australia. Current bi- or trivalent vaccines are effective against the 2 genotypes most strongly associated with cancer (types 16 and 18), which are detected in approximately 95% of HPV-positive oropharyngeal tumors in the United States [32,33], 94% of HPV-positive oropharyngeal tumors in males in Australia [27], and approximately 70% of cervical cancer worldwide. HPV vaccination in Australia is currently provided free of charge to adolescents aged 12-13 years through a school-based program. The goal of early vaccination is to immunize before first exposure to hrHPV [34]. The efficacy and immunogenicity of hrHPV vaccines have proven excellent in several phase 2 and 3 trials involving tens of thousands of women [35]. Few subjects lost their antibodies during the 5-6 years after vaccination, with no breakthrough disease occurring among these individuals. There has been a move to a 2-dose vaccination, which means the effective vaccine coverage in the National HPV Vaccination Program Register in Australia is likely to go up (easier to deliver in 2 rather than 3 doses), although dose spacing is very important. The next generation of nonavalent vaccines [36] has also been approved and is currently under review. Importantly, there is now a growing body of evidence that current vaccines prevent HPV infection at noncervical sites, including the mouth and oropharynx [37,38].

Human Papillomavirus Vaccination Uptake in Indigenous Populations

There are no national-level data available for the uptake of HPV vaccination among Aboriginal and Torres Strait Islander Australians. Data from the first stage of the National HPV Vaccination Program (NHVP) suggest that, in Queensland, coverage among Indigenous girls aged 12-17 years compared with all girls aged 12-17 years was lower with each dose (lower by 4% for dose 1, 10% percent for dose 2, and 15% for dose 3). This pattern was not seen in the Northern Territory, where initial coverage was 17% lower among Indigenous girls, but the course completion rate among those who started vaccination was identical (84%) [39]. Both used data on genital warts, and both reported that the impact of HPV vaccination appeared to be at least as strong in young Indigenous Australians as in non-Indigenous Australians [40,41]. Although there were initially catch-up phases of the NHVP that offered publicly funded vaccination to females aged up to age 26 years and boys aged up to 15 years, these ceased in 2009 and 2014, respectively.

There is now a relatively narrow window in early adolescence when individuals can receive free vaccination; otherwise, the remainder or full vaccine course incurs an additional cost (approximately Aus \$150 per dose). This is likely to be a substantial barrier to uptake among Aboriginal and Torres Strait Islander Australians, as is the possibility of culturally inappropriate, insensitive, alienating, or intimidating aspects of provision in broader health care services [42]. It is worth highlighting, however, that school-based vaccinations reduce disparities, with school retention rates among Indigenous preadolescents being reasonably high at age 12 to 13 years [43].

Efficacy of Human Papillomavirus Vaccination in Older Populations

Wheeler and colleagues [44] conducted a phase 3, double-blind, randomized controlled trial among healthy women older than 25 years to test the hypothesis that the HPV 16/18 vaccine would be efficacious in protecting against infections, cytological abnormalities, and lesions associated with HPV 16/18 and cervical intraepithelial neoplasia level 1+, irrespective of HPV type, and infection with nonvaccine types HPV 31 and HPV 45. After 7 years of follow-up, their hypothesis was proved correct. HPV vaccination is available to females aged up to 45 years and males aged up to 26 years in Australia, at a cost. The level of elective uptake in females who were not eligible to receive vaccination through the publicly funded program is low (11%) [45].

Cost-Effectiveness of Human Papillomavirus Vaccination

Although population-level impact and herd effects following HPV vaccination have been widely documented, cost-effectiveness evaluations in Australia are scarce. Kulasingam et al reported on the cost-effectiveness for females, which supported the original Commonwealth Serum Laboratories application for the vaccine to be included on the National Immunization Program [46]. The cost-effectiveness evaluations that supported HPV vaccination for boys have never been published, although Smith and colleagues [47] evaluated the herd immunity benefits and incremental impact of male vaccinations on cancer, whereas Simms et al [48] evaluated whether cervical screening would remain cost-effective in women offered the next generation nonavalent HPV vaccine in 4 developed countries. To the best of our knowledge, there have been no specific cost-effectiveness evaluations of the optimal strategies for HPV vaccination in Indigenous populations (including the potential for extending vaccination to older ages)—a critical gap in the knowledge base given the higher burden of oropharyngeal and cervical cancer risk among this group.

What Are Utilities and Why Are They Important?

Utilities are fundamental values that represent the strength of an individual's preferences for specific health-related outcomes. Measuring health utilities involves 2 main steps: defining a set of health states of interest and valuing those health states. It is important to estimate utilities in relation to HPV, cervical cancer, and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians because the frame of reference regarding

prevention, screening, and burden of cancer treatment is likely to differ in meaningful ways compared with the non-Indigenous population. Differences may be because of the substantial travel required for many Indigenous Australians and because of time away from family and country. There may be inherent distrust and fear of hospital systems not apparent in non-Indigenous populations, and the specific treatment-associated morbidity may be valued differently. It is important to capture this information that can be used to directly calculate quality-adjusted life years and to, in turn, be translated into health policy regarding Aboriginal patient journeys with primary and secondary prevention for cervical, other genital, and oropharyngeal cancer. Although health state valuations appropriate for modeled economic evaluations have been undertaken for cervical HPV disease including cancer and precancerous lesions [49,50] and for genital warts [51], there is a paucity of information on health state valuations for other HPV cancer states including oropharyngeal cancer. There is a particular dearth of information on HPV-related health state valuations for Aboriginal and Torres Strait Islander Australians.

Study Aims

The aims of this study were as follows:

1. To yield population estimates of the age-specific prevalence of oncogenic genotypes of HPV in the mouth and oropharynx of defined Aboriginal and Torres Strait Islander populations (male and female). *Hypothesis: The prevalence of oral HPV among Aboriginal and Torres Strait Islander Australians will be high compared with national-level estimates.*
2. Using preliminary data from Aim 1, and information on the prevalence of other risk factors for oropharyngeal cancer in the Aboriginal and Torres Strait Islander population, to estimate burden of HPV-related oropharyngeal cancer among Aboriginal and Torres Strait Islander men and women. *Hypothesis: The burden among Aboriginal and Torres Strait Islanders of HPV and related oropharyngeal cancer will be high.*
3. To estimate the impact of HPV vaccination as currently implemented on rates of cervical and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians. *Hypothesis: HPV vaccination will, over time, reduce the burden of cervical and oropharyngeal cancer among Aboriginals and Torres Strait Islanders.*
4. To evaluate efficacy and cost-effectiveness of targeted extended HPV vaccination among Aboriginal and Torres Strait Islander Australians, incorporating the effectiveness against both cervical cancer (in females) and oropharyngeal cancer. Different upper age thresholds for targeted extension will be considered. *Hypothesis: Age-extended HPV vaccination for Aboriginal and Torres Strait Islander Australians will be efficacious; we will estimate an upper age limit at which it would be cost-effective.*

Methods

Study Design

Our overall study design will impose minimal impost on Aboriginal and Torres Strait Islander participants. It involves

testing for carriage of hrHPV in the mouth and oropharynx among 1000 Aboriginal South Australians by simple saliva collection, with follow-up at 12 and 24 months, collection of sexual history at baseline, collection of information for estimating utilities at baseline, genotyping the viruses, statistical analysis (including cost-effectiveness modeling), data interpretation and development of vaccination and clinical therapeutic strategies to better communicate the benefits of HPV vaccination and lifestyle changes in cancer prevention, and approaches to take into account the preferences of Indigenous people in prevention and management of cancer driven by the Aboriginal community.

Ethical Approval

Ethics approval has been obtained from the University of Adelaide Human Research Ethics Committee (H-2016-246). Before being recruited, all participants will be required to sign an informed consent form, which includes consent for the authors to publish the findings in the peer-reviewed scientific literature. The authors confirm that supporting data and material in the study will be made available through Springer Nature's Data Support Services.

Study Population and Recruitment

We will recruit 1000 Aboriginal South Australian male and female adults, with a focus on Port Augusta, Whyalla, Port Lincoln, Mount Gambier, Ceduna, and Adelaide. Census data indicate approximately 22,000 Aboriginal adults reside in these areas. The investigators have a 13-year relationship with key Aboriginal stakeholder groups in these locations, who are willing and excited to be part of the study. Recruitment strategies will be based on those successfully implemented in the past, including the following: establishing service agreements with key Aboriginal community-controlled health organizations, liaising with community champions previously involved in our research, and encouraging word-of-mouth spread of knowledge.

Inclusion and Exclusion Criteria

Participants will be aged 18+ years, identify as being Aboriginal or Torres Strait Islander, and planning to live in South Australia for the next 3 years. Participants not enrolled during the original recruitment period will not be eligible to participate in the follow-up phases.

Collection of Human Papillomavirus and Oropharyngeal-Related Information

Permission to obtain sensitive information from participants will be sought, with relevant information related to alcohol and tobacco use, HPV diagnosis, health behaviors (including HPV vaccination status and sexual behaviors), and social determinants asked through a self-report questionnaire. Data will be collected by experienced Aboriginal research officers.

Collection of Utilities Information

We will design a questionnaire for the utility study, in which all 1000 participants taking part in the oral HPV prevalence study will be asked to indicate preferences (rank and utility scores) for 6 hypothetical states relating to oral HPV testing, precursor oropharyngeal cancer, and early-stage oropharyngeal cancer (including examinations and treatment). On the basis of

standard methods used in the development of utilities, preferences for health states will be measured through ranking (1 through to 6), followed by a 2-stage standard gamble. We will focus on valuing the long-term oropharyngeal cancer health state of the average patient who survives up to 5 years after diagnosis and treatment, which is the most appropriate state for modeling cost-effectiveness of prophylactic HPV vaccination. We will seek to generate utility values for all cancer stages at diagnosis. The process for developing the health states will involve the following: (1) the most common stage(s) of HPV-associated oropharyngeal cancer at diagnosis identified from the literature; (2) the recommended treatment for the relevant stages(s) of oropharyngeal cancer identified and confirmed from published studies; and (3) the more common long-term consequences (applying to $\geq 50\%$ patients) in patients surviving the initial treatment phase described based on the literature, and subsequent refinement by clinical experts involved in managing oropharyngeal cancer [52,53].

Collection of Oral Human Papillomavirus Data

All participants will be asked to provide a saliva sample using a commercially available kit (Omnigene 501; DNA Genotek Inc, Canada) from which microbial DNA for genotyping will be extracted. This involves the participant: (a) not eating or drinking for 30 min before collection; (b) spitting until 2 ml reaches the fill line on the container (takes 2-3 min); (c) closing the lid on the funnel (to release preservative liquid into tube); (d) removing the funnel lid on the container; and (e) placing the small cap on the tube and shaking the tube for 5 seconds. This results in over 100 μg of DNA collection, which is sufficient for the testing required. The sample can be kept at room temperature (for up to 12 months) until collection by the Aboriginal research assistants, who will send it to an appropriate laboratory for analysis. Saliva samples will be collected at baseline, 12 months, and 24 months.

Data Analysis

In brief, the analysis plan for each aim is described below.

Aim 1: To Yield Population Estimates of Oral Human Papillomavirus in the Aboriginal and Torres Strait Islander Population

DNA Extraction and Quality Check

Antonsson and colleagues have evaluated 3 different kits (all semi-automated) for DNA extraction, namely, Promega's Maxwell-16 Viral Total Nucleic Acid Purification Kit, QIAGEN's QIAamp Mini Elute Virus Spin Kit, and QIAamp Blood DNA Mini Kit (QIAcube). We will use the Promega Maxwell viral kit for DNA extraction as the DNA yield and quality was superior compared with the 2 other kits. β -globin polymerase chain reaction (PCR) with the primers PCO3 and PCO4 will be carried out on all samples to ensure that they contain enough cells to detect human DNA, and that no PCR inhibiting agents are present [54].

HPV Type Determination

We will analyze all samples with the optimized general primer (GP)+PCR system that detects most mucosal HPV types and all hrHPV types that have oncogenic potential in mucosal tissue

[54]. All HPV DNA positive samples will be sequenced to confirm viral DNA sequences. For the sequencing, HPV-positive PCR products will be purified with the Agencourt AMPure PCR purification kit in a magnetic 96-ring SPRIplate. Sequencing reactions containing the purified PCR products together with GP+primer and BigDye Terminator will be performed. Sequence reactions will be purified with the Agencourt CleanSEQ dye-terminator removal kit in a magnetic 96-ring SPRIplate. Direct sequencing will be carried out initially. Samples with multiple HPV types will be cloned before sequencing, with at least 5 clones sequenced per sample. Sequence reactions will be analyzed with an automated DNA sequencer (ABI model 3100). The DNA sequences will be compared with available sequences in GenBank through the BLAST server. We have chosen a standard PCR method, which has been used in several projects by Antonsson and proven to be both reliable and reproducible [4,55-57].

Specimen Variables

HPV status and genotypes found will be analyzed. The genotypes will also be divided into low-risk (not found in cancer; eg, HPV-6 and -11) and hrHPV types (found in cancer; eg, HPV-16 and -18). As multiple HPV infections are likely, incident infection will be defined as a new type-specific HPV infection not detected in a previous sample. We will determine the precision of HPV prevalence estimates obtainable with the sample of 1000 in age- and sex-specific subgroups. We will base these estimates on measurements in other populations by age and sex, and then characterize 95% CIs obtainable in the given sample size.

Aim 2: Using Preliminary Data From Aim 1, and Information on Prevalence of Other Risk Factors, to Estimate Burden of Human Papillomavirus-Related Oropharyngeal Cancer Among Aboriginal and Torres Strait Islander Australians

Sufficiently detailed information on oropharyngeal cancer rates overall, or the proportion of oropharyngeal cancers which are HPV-positive, are not available for the Indigenous population. Therefore, these rates will be estimated using published data on HPV-positive and HPV-negative oropharyngeal cancers in the general population [27,58]. Each estimate will be scaled to account for different risk factor prevalences. For HPV-positive cancers, we will use our preliminary findings on the relative prevalence of oral HPV in the Indigenous population compared with that in the general population [57] to scale rates of HPV-positive oropharyngeal cancer. Overall estimates of oropharyngeal cancer will be compared with available published data on the relative incidence of oropharyngeal cancer overall in the Indigenous versus the general population to ensure consistency [5].

Utilities and Costings

We will perform systematic reviews of utilities for oropharyngeal cancer diagnosis, surveillance, surgery, and the diagnosis/treatment of associated cancers. We will also perform systematic reviews of complication rates and associated utilities for surveillance and surgery. Aggregate costs for each step involved in screening, diagnosis, family counseling, referral

and management pathways, and cancer diagnosis and treatment will be collated using methods previously employed by Canfell and colleagues for other cancer-related applications [59,60]. Briefly, detailed clinical pathways for current practice will be described using relevant patterns of care studies and clinical practice guidelines, and will take into account different patterns of care/attendance for treatment among Aboriginal and Torres Strait Islander Australians. Item costs of the component services will be obtained from the Medicare Benefit Schedule Online for outpatient medical services, the latest available National Hospital Cost Data Collection Round for inpatient services and the Pharmaceutical Benefits Schedule Online.

Aim 3: To Evaluate the Impact of Human Papillomavirus Vaccination as Currently Implemented on Oropharyngeal and Cervical Cancer Rates Among Aboriginal and Torres Strait Islander Australians

The results of Aim 2 will feed into an existing model of HPV transmission, vaccination, and natural history developed by Canfell and colleagues through previous grants from Australia's National Health and Medical Research Council (NHMRC). This model has been used extensively for evaluations around HPV and cervical cancer prevention in government-commissioned reports and in 20 journal publications. In the proposed study, this model will be further tailored to the Aboriginal and Torres Strait Islander population. The developed model will be used to make detailed predictions of the impact of HPV vaccination over time on oropharyngeal and cervical cancer among Aboriginal and Torres Strait Islander Australians, including under a range of age ranges for vaccination and dose/uptake assumptions. This will be based on the burden of HPV-attributable oropharyngeal and cervical cancer in the Indigenous population estimated in Aim 2, which will take into account different tobacco smoking prevalence or varied attributable fraction to allow for the higher proportion of HPV-negative tumors in the Indigenous population. Estimates of HPV vaccine uptake in Aboriginal and Torres Strait Islander Australians will be used, in conjunction with available data on HPV vaccine impact in Aboriginal and Torres Strait Islander populations or precursor/proxy outcomes, such as prevalence of infection with vaccine-included types and anogenital warts. We will validate model predictions against these previously reported outcomes [41,42].

Aim 4: To Evaluate Efficacy and Cost-Effectiveness of Targeted Extended Human Papillomavirus Vaccination on Oropharyngeal Cancer Among Aboriginal and Torres Strait Islanders, Incorporating the Effectiveness Against Both Cervical Cancer (in Females) and Oropharyngeal Cancer

We will use data from the literature review and utility estimations in Aim 2 to inform model assumptions on the demographics and risk profile of the population. To achieve higher coverage in this group, we will estimate impact and cost-effectiveness of funding extended catch-up vaccination for Aboriginal and Torres Strait Islander Australians (for those who did not receive the vaccine through the school-based program). A range of potential extended catch-up strategies will be considered, eg, funding HPV vaccination for females \pm males

aged up to 18, 25, 30, or 45 years who have not already received a full course. We will consider both first and second generation HPV vaccines and also consider strategies involving revaccination of individuals who have already received the first generation vaccine with the second generation vaccine. We will also consider different potential delivery mechanisms, eg, via Aboriginal health services and/or other community providers. For each analysis, a large “virtual” sample of the Aboriginal and Torres Strait Islander population will be simulated. Each evaluation will then use all fitted parameter sets to derive a baseline result and 95% CI. These evaluations will simulate 10,000 individuals. All evaluations will be accompanied by extensive sensitivity analysis, using one-way and probabilistic sensitivity analysis techniques that will take into account the full range of identified fitted parameter sets. For each strategy, we will calculate a number of measures of effectiveness, including change in cancer incidence, mortality, life years saved, and quality-adjusted life years gained. We will also estimate absolute case numbers based on population projections available by age, sex, and calendar year for ASTI Australians. We will assess morbidity via calculation of quality-adjusted life years and calculate complication numbers from surveillance and surgery. We will take into account varying rates of attendance for treatment in the Indigenous population [61], but consider a range of assumptions in sensitivity analysis. We will provide detailed predictions of health resources utilization, including numbers of tests, biopsies, and treatments. We will assess costs of diagnosis, surveillance and cancer treatment, and the total budget impact for each year from 2017 to 2030. We will calculate incremental cost-effectiveness ratios for both life years saved and quality-adjusted life years. If results suggest that extended HPV vaccination among Aboriginal and Torres Strait Islander Australians is not cost-effective at any age threshold, we will perform threshold analysis to determine the cost at which extended HPV vaccination to different upper age thresholds becomes cost-effective.

Ethical Approval

Ethical approval for this study has been obtained by the University of Adelaide Human Research Ethics Committee (H-2016-246).

Results

Participant recruitment for this study commenced in February 2018 and enrollment is ongoing. The first results are expected to be submitted for publication in 2019.

Discussion

Study Overview

Oropharyngeal cancer is an important cancer affecting Aboriginal and Torres Strait Islander Australians at a higher

rate than other Australians. Infection with hrHPV is a significant risk factor for oropharyngeal cancer. HPV vaccination is effective against the 2 most common types of hrHPV, with some promise that current vaccines may prevent oral infections (potentially reducing the risk of oropharyngeal cancer). Given the elevated risk of HPV-related cancers in this group, it may be reasonable to extend the comparatively brief timeframe (when aged 12-13 years) in which Aboriginal and Torres Strait Islander Australians can access an otherwise costly vaccine via public funding. The project will have a number of important outcomes. Synthesis of evidence will directly support estimates of the burden of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians and the effectiveness and cost-effectiveness of prevention. This will be important for health services planning, and for Aboriginal health worker and patient education. The project provides a key example of how carefully calibrated, data-driven disease models can integrate with Aboriginal community views and expectations to estimate disease burden and to guide policy decisions.

Study Strengths

The strengths of the study include it being the first to obtain and link all the information on cervical and oropharyngeal cancers via modeling (possibly in any population but certainly for the Australian Aboriginal and Torres Strait Islander population) and the focus on engagement, enabling community and individual preferences to play a large role in decision making for Aboriginal and Torres Strait Islander Australians. Burger and colleagues investigated the impact of HPV on 6 HPV-associated cancers, including cervical and oropharyngeal cancer, among 5 ethnic groups in the United States, one of which included Native American/Alaskan Natives [62].

Study Limitations

The limitations include the sample frame for oral HPV prevalence assessment being pragmatic, ie, utilizing convenience sampling methodology rather than attempting to be representative. Although there is a risk of sampling bias, the efforts required to obtain a representative sample are recognized as being both expensive and time-consuming [63]. Additionally, it is recognized that oral HPV measurement through saliva sampling is blunt as it does not provide a direct measure of HPV exposure at each potential cancer site. Finally, as in any modeled assessment, assumptions about future vaccination and screening coverage need to be made, but we remain committed to engaging the Aboriginal and Torres Strait Islander community in consultation about such assumptions via the study's Aboriginal Reference Group.

Acknowledgments

This study is governed by an Aboriginal Reference Group, who will oversee the orchestration, delivery, and feedback of the study findings as it relates to the health and well-being of Aboriginal and Torres Strait Islander Australians. The authors sincerely

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Authors' Contributions

All authors are named investigators on the project; they all contributed to the intellectual input of the study design and in writing this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer Review Assessment from Australia's National Health & Medical Research Council

[[PDF File \(Adobe PDF File\), 279KB - resprot_v7i6e10503_app1.pdf](#)]

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Abbreviations

GP: general primers

HPV: human papillomavirus

hrHPV: high-risk human papillomavirus

NHMRC: National Health and Medical Research Council

NHVP: National HPV Vaccination Program

PCO3: (5'CTTCTGACACAACCTGTGTTCACTAGC3') oligonucleotide

PCO4: (5'TCACCACAACCTTCATCCACGTTCACC3') oligonucleotide

PCR: polymerase chain reaction

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Proposal

A Putative Role of Apolipoprotein L1 Polymorphism in Renal Parenchymal Scarring Following Febrile Urinary Tract Infection in Nigerian Under-Five Children: Proposal for a Case-Control Association Study

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Abstract

Background: Although urinary tract infection (UTI) resolves with prompt treatment in a majority of children, some children, especially those aged less than 5 years, also develop renal parenchymal scarring (RPS). RPS causes high blood pressure that may lead to severe chronic kidney disease and end-stage renal disease (ESRD). Although the risk of UTI is higher in white children than in black children, it is unknown whether RPS is more common in white children than in black children as data are scarce in this regard. A common genetic predisposition to kidney disease in African Americans and the sub-Saharan African blacks is the possession of apolipoprotein L1 (APOL1). APOL1 risk variants regulate the production of APOL1. APOL1 circulates in the blood, and it is also found in the kidney tissue. While circulating, APOL1 kills the trypanosome parasites; an increased APOL1 in kidney tissues, under the right environmental conditions, can also result in the death of kidney tissue (vascular endothelium, the podocytes, proximal tubules, and arterial cells), which, ultimately, is replaced by fibrous tissue. APOL1 may influence the development of RPS, as evidence affirms that its expression is increased in kidney tissue following UTI caused by bacteria. Thus, UTI may be a putative environmental risk factor responsible for APOL1-induced kidney injury.

Objective: The aim of this proposal was to outline a study that seeks to determine if the possession of two copies of either G1 or G2 APOL1 variant increases the risk of having RPS, 6 months following a febrile UTI among Nigerian under-five children.

Methods: This case-control association study seeks to determine whether the risk of RPS from febrile UTI is conditional on having 2 APOL1 risk alleles (either G1 or G2). Cases will be children with a confirmed RPS following a febrile UTI. Controls will be age-, gender-, and ethnic-matched children with a febrile UTI but without RPS. Children with vesicoureteral reflux and other congenital anomalies of the urinary tract are to be excluded. Association between predictor variables (ethnicity, APOL1 G1 or G2, and others) and RPS will be tested at bivariate logistic regression analyses. Predictors that attained significance at a *P* value of .05 will be considered for multiple logistic regressions. Likelihood-based tests will be used for hypothesis testing. Estimation will be done for the effect size for each of the APOL1 haplotypes using a generalized linear model.

Results: The study is expected to last for 3 years.

Conclusions: The study is contingent on having a platform for undergoing a research-based PhD program in any willing university in Europe or elsewhere. The findings of this study will be used to improve the care of African children who may develop RPS following febrile UTI.

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KEYWORDS

child; humans; cicatrix; apolipoprotein L1; research design; urinary tract infections; kidney

Introduction

Background

Approximately 7% to 8% of girls and 2% of boys have a urinary tract infection (UTI) during the first 8 years of life [1]. Although febrile UTIs have the highest incidence during the first year of life in both sexes, nonfebrile UTIs occur predominantly in girls older than 3 years [1]. Renal parenchymal scarring (RPS) is a common complication of febrile UTI, and it occurs in 10% to 30% of children with febrile UTIs in developed countries [2]. RPS is a precursor of poor renal growth, hypertension, chronic kidney disease (CKD) and end-stage renal disease (ESRD) that are seen in adulthood [2]. Although RPS is less frequently encountered in developed countries because of improvement in overall health care and close follow-up of children with UTI [2], most cases of UTI in developing countries, including Nigeria, are still being missed, and follow-up of children for RPS is virtually nonexistent [3]. The prevalence of RPS complicating febrile UTI in Nigerian children, therefore, remains unknown. Although the incidence of ESRD is unknown in Nigeria, there is a strong indication that hypertension contributes substantially to it [4-6]. The overall prevalence of hypertension among Nigerians ranges from 0.1% to 17.5% in children and 2.1% to 47.2% in adults [7]. This study becomes relevant as UTI or RPS may have been a precursor of hypertension in the Nigerian population.

The clinical features of UTI in childhood are often different from those found in adults and are frequently nonspecific [3]. Therefore, many cases of UTI are missed, especially in under-fives, among whom the risk of RPS is even greater [2,3,8]. Some children with UTI present only with fever without a clear source of infection or systemic symptoms [9]; fever is also the commonest symptom of UTI [10]. In addition, the presence of another source of fever does not exclude the probability of UTI [8]. Although the available Nigerian studies have reported the prevalence of UTI among febrile under-five children to be between 9% and 37.1%, longitudinal follow-up to determine the risk of renal scars and other complications of febrile UTI is unknown [3,11,12]. This may also be because of lack of imaging modalities such as the dimercaptosuccinic acid (DMSA) scan. DMSA scan is the gold standard for diagnosing RPS [9].

Although the pathogenic mechanism of renal scarring following acute pyelonephritis (APN) is not well understood, the combined presence of congenital anomalies (vesicoureteral reflux, VUR and renal hypodysplasia), inflammation seen in pyelonephritis, and genetics may interact to result in scar formation [13]. The host innate immune response serves as the primary factor for the defense of the kidney [14]. The innate immune system of the kidney in response to invading bacteria involves peptides with antimicrobial properties, renal epithelial cells, cytokines and chemokines, neutrophils, and pattern recognition receptors (PRRs) [14]. The most studied PRR is the toll-like receptor 4 (TLR4), which upon recognizing gram-negative bacteria's lipopolysaccharide, signals intracellular pathways that leads to

transcription of proinflammatory molecules, including chemokines and cytokines, which then activate and target neutrophils to the site of infection [13-18].

These chemokines and cytokines include the interleukin 6, chemokine ligand 2 (CXCL2), interferon β 1, CXCL8 (also known as interleukin 8), the interferon regulatory factor 3 (IRF3), interferon-gamma (IFN- γ), tumor necrosis factor (TNF), transforming growth factor beta (TGF- β), and vascular endothelial growth factor (VEGF) [13-18]. TGF- β and VEGF are particularly notable for RPS as they modulate the glomerular and tubule-interstitial scarring. While TGF- β mediates progression of renal fibrosis in association with activation of angiotensin II (ANG II), VEGF enhances the proliferation of vascular endothelial cells, angiogenesis, and microvascular permeability [19-21]. Thus, although bacteria play a crucial role in initiating an inflammatory response during renal colonization, renal damage from APN seems to be primarily because of an inflammatory response of the host rather than an invasion of pathogens [13].

With the exception of antimicrobial peptides and epithelial cells that have not been well studied, single gene defects or variations in various genes have been shown to affect most of the other innate immune expression and response to invading bacteria [14]. For example, a reduced CXCR1 expression is a risk factor for APN, and variations in the CXCR2 receptor and the CXCL8 chemokine lead to UTI susceptibility [22,23]. Low TLR4 expression and signaling protects the host against symptomatic UTI and promotes the development of asymptomatic bacteriuria [24,25]. IRF3_925 A/G and _776 C/T polymorphisms involved in neutrophil recruitment are strongly associated with febrile UTI susceptibility [26]. Genetic polymorphisms in both TGF- β and VEGF are also well noted for the acquisition of RPS [27,28]. The TGF β 1_509 T allele and the VEGFA_406 CC genotype are associated with a risk of renal scarring after UTI [29]. Polymorphism in the intercellular adhesion molecule 1 exon 4 was less common in patients who developed RPS in one study [30]. Polymorphisms of the angiotensin-converting enzyme and ANG II type 1 receptor genes are also implicated in the risk of RPS acquisition [31,32].

As observed already, although several significant mutations [22-32] have been identified in the innate immune response that may explain the risk of UTI or RPS, much is still to be discovered, and further research is needed to elucidate and validate host factors and genetic variations that may predispose to UTI or RPS [33]. In the quest to summarize the genetic host factors that predispose to RPS, a 2011 meta-analysis of cumulative studies showed only a modest association between RPS after UTI and the vasomotor genes involving the angiotensin-converting enzyme insertion or deletion polymorphisms and the inflammatory genes involving TGF- β 1 c.-509 T>C polymorphisms [33]. Although heterogeneity among the studies was large, some gene expression differences were observed that could not be explained by differences in study design, and a few possible candidate genes have been

investigated [33]. The role of inflammatory genes in RPS also warrants further investigation, as Hewitt et al also demonstrated that early treatment of APN in infants and young children had no significant effect on the incidence of subsequent renal scarring in an Italian cohort [34]. Bearing the foregoing in mind, apolipoprotein 1 genetic variant is suggested as the risk factor in the pathogenesis of RPS following febrile UTI.

African Americans have a three-fold higher lifetime risk of ESRD as compared with non-Hispanic whites because of a higher incidence of CKD and glomerulonephritis [35,36]. Recent studies also suggest that blacks living in sub-Saharan Africa (African blacks) may have a similarly high predilection to kidney disease as do African Americans, and these two populations (African Americans and African blacks) may share a common genetic predisposition [37,38]. Two apolipoprotein L1 (APOL1) susceptibility gene variants (G1 and G2) have been identified, with 88% higher risk of CKD progression in African Americans, and have also been suggested for the higher predilection of kidney disease in African blacks [39]. The APOL1 gene variants encode for circulating APOL1, which functions as a trypanolytic factor capable of killing the trypanosome parasites in the human serum [40-43]. People who have at least one copy of either the G1 or G2 variant are resistant to infection by trypanosomes, but people who have two copies of either variant are at an increased risk of developing nondiabetic kidney diseases, including hypertension-attributed end-stage kidney disease (ESKD), HIV-associated nephropathy (HIVAN), and focal segmental glomerulosclerosis (FSGS) [37,44]. The prevalence of the risk alleles in African Americans with these kidney diseases shown in recent studies are 67% in HIVAN, 47% in hypertension-attributed ESKD, and 66% in FSGS [37,44]. FSGS is a pattern of injury consisting of a sclerotic area made up of extracellular matrix and fibrous tissue; curiously, secondary FSGS can follow any injury that results in a substantial decrease in nephron number as seen in severe advanced primary tubulointerstitial diseases such as chronic obstruction or pyelonephritis [45].

Although possession of the APOL1 risk variants in an autosomal recessive manner increases susceptibility to nondiabetic kidney disease, not all people who possess these variants develop kidney disease, which indicates that another factor may initiate progression of kidney disease [45,46]. In addition, several studies suggest that one or both of the APOL1 risk variants may be gain-of-function mutations rather than loss-of-function mutations as the recessive mode of inheritance would suggest [46,47]. Thus, the kidney risk variants APOL1 may have acquired toxic properties rather than lost attributes essential for kidney health [47]. The APOL1 is a 398 amino acid protein with five functional domains, including the S domain-secretory signal, the membrane-addressing domain that serves as pH sensor and regulator of cell death, the BH3 domain associated with programmed cell death, the pore-forming domain, and the serum resistance-associated binding domain that confers resistance to trypanosoma brucei [48].

For the following reasons, APOL1 is hypothesized to play a role in the pathogenesis of RPS, as febrile UTI may be a second-hit insult for the APOL1 kidney disease risk variants:

1. APOL1 is resident in vascular endothelium, podocytes, proximal tubules, and arterial cells [49,50].
2. Two renal transplantation studies suggest that the APOL1 kidney risk allele association is mediated by the gene product isoform that is endogenously expressed within the kidney and not the circulating APOL1 [51,52].
3. APOL1 is a member of the family of BH3-only proteins that interacts with the family of Bcl2 proteins to help regulate their function in autophagy and apoptosis [53,54].
4. Although apoptosis is a beneficial process for the host in lower UTI as it results in exfoliation of the superficial cells of the multilayered epithelium and thus the eradication of the bacteria attached to and invaded into the cells, however, where the epithelium is single-layered and close to the underlying kidney tissue and blood vessels, apoptosis is more likely to be part of a deleterious cycle of tubular atrophy, cytolytic events, and renal scarring [55,56].
5. The expression of APOL1 in human embryonic umbilical vein endothelial cells can be induced by lipopolysaccharide [56] and by circulating inflammatory cytokines, including IFN- γ and TNF α [55], which supports the role of APOL1 in up-regulating the innate immune response to UTI.
6. APOL1 is involved in innate immunity, which is the primary response of the human host to bacterial invasion of the urinary tract or kidney tissue. It is up-regulated by proinflammatory cytokines gamma interferon and TNF α [57]. These molecules are known to attract neutrophils to the kidney during infection, and hence, the consequent RPS that may occur, as explained previously [15].
7. In cell culture, interferon and toll-like receptor agonists increased APOL1 expression by up to 200-fold; in some cases with the appearance of transcripts not detected under basal conditions. PolyI:C, a double-stranded RNA TLR3 agonist, increased APOL1 expression by up-regulating interferon directly or through an interferon-independent, IRF-3-dependent pathway [46].
8. The innate immune response to bacterial UTI also involves IRF-3 stimulating pathway, and there may be an increased APOL1 expression [46]. IRF3 _925 A/G and _776 C/T polymorphisms involved in neutrophil recruitment are strongly associated with febrile UTI susceptibility [46].
9. Little is still known about the roles of APOL1 in kidney disease. Over time, there has been an extension in the spectrum of APOL1-associated kidney diseases, including systemic lupus erythematosus [57,58], membranous nephropathy [59], sickle cell disease [60], and even an association of two risk variants of APOL1 in diabetic patients with CKD [61,39].

This study hypothesizes that APOL1 may be associated with RPS of UTI and that UTI is a trigger that determines RPS in susceptible individuals with APOL1 risk variants.

In addition to the limited availability of DMSA scanner, the issues of cost and exposure to radiation in children have prompted researchers to seek clinical or laboratory predictors of RPS. Most of the studies on the prevalence and clinical predictors of RPS following UTI were conducted in Europe, North America, Australia, and the Middle East and in Asia, with little or no data from sub-Saharan Africa, a region of the

world where the APOL1 risk alleles are highly prevalent [62-73]. The researchers in these other continents have reported the risk factors for renal scarring in children with UTI to include age at diagnosis, gender, delayed treatment, recurrent infections, peak of fever, laboratory indices of inflammation (total white blood cell, WBC, count; procalcitonin, PCT; and C-reactive protein, CRP, concentration), the extent of renal parenchymal lesions, race or ethnicity, and the presence of VUR [62-73]. In fact, in a systematic review by Shaikh et al, VUR was found to be an independent risk factor for RPS [74], and VUR, notably, is also the most important risk factor for RPS following UTI [30]. Although VUR is rare in black children compared with their white counterparts [75], blacks are known to be more prone to kidney damage [37,38]; so it is possible that this predisposition is by far more potent and basically removes the advantages conferred by the lower rates of VUR. In addition, Atefi et al [76] and Benador et al [77] did not find age less than 5 years to be a predictor of RPS in their studies, and other authors also did not find any risk factor predictive of RPS in their studies [78,79]. Furthermore, in a meta-analysis by Faust et al, RPS was reported more among children in Asia than in the Middle East or in Australia [80], indicating a racial predisposition to RPS.

In view of the conflicting reports regarding the predictors of RPS among children with UTI, carrying out a well-designed, highly powered prospective cohort study to determine the risk of acquiring RPS in Nigerian children with a febrile UTI will contribute to the existing data of RPS in children with UTI. The findings of this study will for the first time provide information on the susceptibility factors ethnic sub-Saharan Africans may have for the development of RPS following a febrile UTI.

Africa, and in fact Nigeria, has complex populations and variations in climate, diet, and exposure to infectious diseases, which makes it a good setting for studying diversities in human genetics and phenotypes [81]. In this way, this work proposes to study the effects of APOL1 kidney risk variants on the acquisition of RPS following a febrile UTI in Nigerian under-five children. A better understanding of the risk factors for RPS following a febrile UTI would allow for individualized care models that would allow for a better prediction of RPS.

The overarching hypotheses are that RPS is a common complication of a febrile UTI in Nigerian under-fives and that the possession of APOL1 kidney risk variants increases the risk of RPS in these children. The study also proposes that clinical and laboratory predictors of RPS exist among children presenting with a first febrile UTI.

Specific Aims and Hypotheses

Specific Aim 1: To Determine the Prevalence of Urinary Tract Infection Among Febrile Under-Five Children Attending the Emergency Pediatric Unit of the National Hospital, Abuja, Nigeria

Hypothesis 1: UTI is common among Nigerian under-fives with fever, with or without a specific source of the fever.

The presence of UTI among Nigerian children aged between >1 month and 60 months, presenting with axillary temperature

$\geq 37.5^{\circ}\text{C}$ at the emergency pediatric unit (EPU) shall be determined. Children less than 1 month of age shall be excluded because their clinical presentations are unique. This is because they may present with hypothermia instead of fever [82]. There is also the need for immediate empiric antibiotics for the febrile neonate [82]. Also to be excluded are children who have been treated for UTI, children who have been on antibiotics 2 weeks before presentation, and children with known a neurological lesion causing bladder dysfunction, or those with a known stone disease. Urine collection will occur before the commencement of antibiotics if indicated for the presenting fever, as a single dose of an effective antibiotic rapidly sterilizes the urine. A midstream, clean-catch specimen will be obtained from children who have urinary control. A properly labeled universal bottle will be used to collect the urine sample. Prior cleansing of the perineum or urethral orifice will be done. In the infant or child unable to void on request, the urine specimen for culture will be obtained by suprapubic aspiration or urethral catheterization, and the procedures will follow the standard sterile technique. Suprapubic aspiration will also be the method of choice for obtaining urine from uncircumcised boys with a redundant or tight foreskin, from girls with tight labial adhesions, and from children of either sex with clinically significant periurethral irritation [2]. When tests on the urine will not be performed within the first hour of urine collection, urine will be stored in the refrigerator (at 4°C) and will be tested within 4 hours of storage in the refrigerator [8,83]. Urine refrigerated will be kept at room temperature for 15 min before tests will be performed on them [83]. The urine so collected will be divided into two equal parts—one part for urine culture and the other part for dipstick urinalysis, enhanced urinalysis, and automated urinalysis. UTI will be defined as a positive test result for pyuria by either microscopy (≥ 5 WBCs per high-power field, [HPF] in uncentrifuged urine specimen) or dipstick test (positive leucocyte esterase test) and a positive growth on culture of at least 50,000 colony-forming unit (CFU) per mL of a single uropathogen in urine specimen obtained by catheterization or greater than 100,000 CFU per mL of a single uropathogen in clean-catch urine specimen or any uropathogen growth in urine obtained suprapubically [84]. Urine confirmation for UTI shall be done at the microbiology laboratory of the National Hospital, Abuja, and urinary inoculation on culture media and interpretation shall be done by a consultant microbiologist. Antibiotic treatment will be started empirically for all children as soon as possible based on epidemiology data at the National Hospital and, if required, changed to appropriate antibiotics according to the results of the sensitivity tests. A study proforma will be used to obtain the following information from the subjects: (1) sociodemographic data: age, gender, place of residence (urban or rural), ethnicity or tribe, and socioeconomic status of the household; (2) past medical history: prior use of antibiotics, past history of UTI, family history of recurrent UTI, family or subjects' history of congenital anomaly of the urogenital tract (ie, VUR), prior history of worm infestations, history of constipation, and history of breastfeeding in the first 6 postnatal months; (3) symptom: jaundice, poor feeding, vomiting, diarrhea, irritability, strong smelling urine, abdominal pain, flank or back pain, irritability, dysuria, frequency, dribbling, poor stream, or straining to void; (4) signs: acutely

ill-looking or not, degree of fever (≥ 37.5 - 38.5 , >38.5 - 38.9 , ≥ 39) and duration of fever before presentation (0-5 days, 6-14 days, >14 days), undernutrition as determined from anthropometric (height or length, weight, midarm circumference, occipitofrontal circumference) measurement, tenderness of the flank or costovertebral angle, suprapubic tenderness, abdominal tenderness, circumcision, signs of irritation on the external genitalia, pinworms, vaginitis, trauma, or sexual abuse; and (5) comorbidity: malaria, HIV, sickle cell disease, sepsis, upper respiratory tract infection or otitis media, pneumonia, nephrotic syndrome (NS), viral exanthema, malignancies, etc.

Specific Aim 2: To Determine the Prevalence of Renal Parenchymal Scarring Among Febrile Under-Five Nigerian Children With a Confirmed Urinary Tract Infection

Hypothesis 2: RPS is a common complication of UTI among febrile under-five Nigerian children.

RPS shall be determined with technetium Tc 99m DMSA renal scintigraphy. However, as studies have demonstrated that many abnormalities seen in DMSA scan done at 2 weeks resolve over time, and that little benefit exists in doing DMSA scan at 2 weeks, DMSA scan will be performed 6 months after the treatment for UTI to confirm or rule out chronic parenchymal scarring [8,85,86]. The DMSA scanning will be done at the National Hospital, Abuja, under the supervision of a consultant radionuclide physician. A kidney without uptake defect and 45% or greater relative (split) function will be classified as normal (DMSA class 0), and a kidney with decreased or absent uptake in one or more areas, or relative function less than 45% will be considered abnormal. The extent of kidney damage will be graded arbitrarily as class 1—uptake defect with 45% or greater relative function, class 2—40% to 44% relative function, and class 3—less than 40% relative function. In cases of bilateral renal damage, the kidneys will be individually classified by uptake defect extent. In cases of unilateral duplication, the expected mean normal split function will shift from 50% to 54%. Thus, the lower limit of normality will be considered at 49% [87].

Specific Aim 3: To Perform Genotyping and Analysis of Known Disease Susceptible Variants in the Apolipoprotein L1 Gene in Children With Renal Parenchymal Scarring Following Febrile Urinary Tract Infection

Hypothesis 3: APOL1 nephropathy risk variants G1 and/or G2 are associated with RPS following a febrile UTI.

For DNA samples, blood samples will be obtained from all children with confirmed UTI. We shall collect about 1.5 mL of whole venous blood. DNA will be extracted using labeled collection tubes for blood. All samples will be allocated a unique identifier and will be stored at -4°C . The blood samples shall be shipped to a reputable diagnostic molecular laboratory in London, United Kingdom. The new *Axion Genome-Wide Pan-African Array Set* will be used for the genome-wide genotyping. At the least, three specific APOL1 candidate single nucleotide polymorphisms (SNPs) will be genotyped, including

rs73885319 and rs60910145 in G1 and rs71785313 in G2 [51]. Cases would then be children with no VUR who develop RPS at 6 months following UTI, and controls will be children with confirmed UTI but without RPS scarring at 6 months.

Specific Aim 4: To Determine the Association Between Vesicoureteral Reflux and Febrile Urinary Tract Infection

Hypothesis 4: VUR is common in Nigerian under-fives with febrile UTI.

Micturating cystourethrogram (MCUG) shall be performed at 2 weeks of follow-up on children with confirmed UTI who also have abnormal renal and bladder ultrasound (RBUS) features, including hydronephrosis, scarring, high-grade VUR, or obstructive uropathy, in line with the 2011 American Academy of Pediatrics Clinical Practice Guideline that took into consideration the fact that MCUG is an uncomfortable, costly procedure that involves exposure to radiation [8]. The RBUS shall be done routinely at the first contact for all children with confirmed UTI.

At this time point (2 weeks), the MCUG will be done when the child must have received the full course of antibiotics treatment for the UTI. VUR will be graded into five classes as follows [88]: grade I—only fills the ureter but no dilation; grade II—fills ureter, pelvis, and calyces but without dilation and normal appearing calyces; grade III—mild or moderate dilation of the ureter and pelvis but no or only slight blunting of the fornices; grade IV—moderate dilation or tortuosity of the ureter with mild dilation of renal pelvis and calyces and blunting of the calyces; and grade V—gross dilation and tortuosity of the ureter, gross dilation of renal pelvis and calyces, and papillary impressions are no longer visible in most calyces.

The RBUS and the MCUG will be done by a consultant radiologist at the radiological department of the National Hospital, Abuja.

Specific Aim 5: To Assess the Association Between Predictor Variables Assessed at the Time of the Febrile Urinary Tract Infection and the Development of Renal Parenchymal Scarring at 6 Months of Follow-Up

Hypothesis 5a: Clinical and laboratory variables exist that can predict the risk of RPS at 6 months following a febrile UTI.

Hypothesis 5b: Serum TNF- α is more sensitive and specific than IFN- γ , PCT, CRP, erythrocyte sedimentation rate (ESR), and polymorphonuclear cell count in predicting renal RPS following a febrile UTI.

A comprehensive data of the sociodemographic, clinical signs and symptoms, examination findings, and the presumptive diagnoses will be collected on the first encounter for each child after informed consent has been obtained from the parents or caregivers of the children. About 2 mL of blood will be collected for complete blood counts, ESR, CRP, PCT, TNF- α , and IFN- γ . Other routine investigations will be as for the diagnostic work-up toward the presumptive diagnosis. The following factors will be considered for inclusion in the prediction model for RPS:

age, sex, ethnicity, measured temperature at the time of diagnosis, duration of fever before presentation, grade of VUR, the organism isolated from culture (*Escherichia coli* vs other), results of renal ultrasonography (normal vs any abnormality), and levels of inflammatory markers (CRP, ESR, TNF- α , IFN- γ , PCT, and polymorphonuclear cells).

Elevated acute phase reactants will be taken as follows: CRP >40 mg/L [89], ESR >20 mm/hour [90], PCT \geq 0.5 ng/mL [91], and polymorphonuclear cells count >60% [92].

PCT is produced by the liver and peripheral blood mononuclear cells and modulated by lipopolysaccharides and sepsis-related cytokines. PCT is very specific for bacterial infection and helps to distinguish between viral and bacterial infections, which are particularly useful in children [93].

Although TNF- α and IFN- γ are both immunomodulating and proinflammatory cytokines, TNF- α secretion by activated macrophages is via bacterial lipopolysaccharide, whereas, IFN- γ is critical for innate and adaptive immunity against viral, some bacterial, and protozoal infections [94,95]. Thus, this study proposes that TNF- α may be more specific and sensitive than IFN- γ and other proinflammatory proteins in detecting the host's inflammatory response to invading bacterial UTI and hence, the consequent RPS.

Expected Impact of Study

This study is important because it is coming at a time when genetic studies have started to explain the differences in the predisposition to kidney diseases in blacks compared with white. The study seeks to unravel for the first time the potential role of APOL1 kidney risk alleles in the evolution of RPS consequent on febrile UTI. The prevention of RPS is the most important goal of all therapies for childhood UTI, and if APOL1 kidney risk variants are shown to be associated with RPS, it will offer less invasive genetic biomarkers for predicting children who will develop RPS following UTI. This approach will reduce the need for urinary tract imaging that is expensive and exposes children to toxic radiation. This study will also offer an opportunity for clinical and translational research of kidney disease, as it will expose the researcher to training in genomic science and genetic studies.

Significance of Study

The significance of study is as follows:

1. Although children with UTI tend to present with fever, it is often difficult on clinical grounds to distinguish UTI from other febrile illness. This makes UTI one of the most often missed diagnoses in the pediatric wards in developing countries [96,97]. UTI, whether confirmed or undiagnosed, has greater significance in childhood than in adults as most renal scars occur after such infections in the first 5 years of life [6-8,98]. The finding of this study would add to the body of evidence, suggesting that all children aged less than 5 years presenting with fever at the EPU be screened for UTI.
2. The long-term complications of febrile UTI (APN) have been previously studied, and they include the risk of RPS, hypertension, preeclampsia, and ESKD that may ultimately

require dialysis or renal transplantation [99]. These long-term complications have been linked with the evolution of RPS. This will be the first comprehensive study that would determine the clinical and laboratory risk factors of RPS acquisition following a febrile UTI in African children, resident in Nigeria. The study may produce an easily implementable clinical and laboratory prediction models that could be used to identify children at risk for renal scarring. Furthermore, if the risk of developing RPS following a febrile UTI is sufficiently high, it would make necessary the request for DMSA scan a worthwhile and cost-effective diagnostic follow-up in a low-income country such as Nigeria.

3. Some researchers did not find any clinical predictors of RPS following UTI [77,78]; a recent meta-analysis by Shaikh et al in 2014 also could not make a conclusive recommendation for the use of PCT, CRP, and ESR [65] in predicting APN from cystitis because of paucity of studies. The target population of the present research will therefore add to the pool of information that seeks to determine the potential role of acute phase reactants, including ESR, CRP, PCT, TNF- α , and IFN- γ in predicting the risk of renal parenchymal involvement and subsequent RPS in febrile children with UTI. In particular, the research would seek to determine the role of TNF- α and IFN- γ in predicting RPS, as these proinflammatory cytokines are known to up-regulate the expression of APOL1 in the kidney tissues [55,56].
4. RPS following UTI is an important cause of renal morbidity in children. Studies have shown that the intensity of the inflammatory response following infection is related to the risk of RPS. However, genetic variability in this response has not been well studied [30]. This study proposes that possession of G1 and/or G2 APOL1 kidney risk alleles pose a "gain-of injury" in the evolution of RPS following a febrile UTI. If APOL1 risk variants are found to be associated with RPS, it would make a strong case of assaying for APOL1 risk variants as a genetic biomarker for RPS among febrile black African under-five children with UTI. It would eliminate the need for exposure to expensive DMSA irradiation for diagnosing RPS.
5. VUR is one of the most common inherited diseases of the genitourinary tract in children. The incidence of primary VUR is 1% in normal infants, whereas it is 30% in infants presenting with UTI [100]. VUR notably is also the most important risk factor for RPS following pyelonephritis [30]. However, in a Nigerian 5-year prospective study that involved 699 patients with renal disorders, although UTI accounted for most of the renal disorders (68.9%), no child was found with VUR [101]. This study will add to the pool of data seeking to determine the contribution of VUR to UTI and subsequent RPS in Nigerian children.
6. Presently, there is a paucity of epidemiologic, genomics, and translational studies of kidney disease among Africans. There is inadequate knowledge and exposure to genetic and translational longitudinal studies. The future of predictive, preventive, and individualized medicine in Africa is therefore gloomy but could be remedied by training more clinician researchers. Hopefully, there is a lot to be gained

by the researcher in terms of training and exposure in the process of executing this research work.

The researcher's capacity to conduct this study is presented in [Multimedia Appendix 1](#).

Methods

Experimental Design

This is a prospective, observational, longitudinal, case-control cohort study involving febrile under-five children presenting at the EPU of the National Hospital, Abuja. The conceptual framework is as depicted in [Multimedia Appendix 2](#). The initial framework was originally from the schematic illustration of the pathogenesis of UTI by Johnson et al [102].

Study Environment

The National Hospital is located in Abuja, the Federal Capital Territory of the Federal Republic of Nigeria. Abuja is located in the North Central Geo-Political Zone of Nigeria. It occupies a land area of 7753.9 square kilometers [103]. Abuja grew by 139.7% from 2000 to 2010, making it the fastest growing city in the world [104].

Target Population

As of 2016, Abuja's population is estimated at 6 million persons [105]. Abuja is a newly created city where all Nigeria's 250 ethnic tribes are expected to live together in harmony. The indigenous inhabitants of Abuja are the Gbagyis, the Bassas, the Gwandaras, the Gedes, the Ganaganas, and the Koros; however, the major tribes of Hausa, Yoruba, and Igbo also reside in the city in large numbers. All the inhabitants of Abuja are expected to patronize the National Hospital, situated at the Independence Avenue, Phase 2, Abuja. The city would, therefore, provide a good repository of diverse genetic representation suitable for testing the influence of APOL1 kidney risk variants on RPS acquisition. The National Hospital was established under Decree 36 of 1999 but was commissioned on May 22, 1999 [106]. It is a tertiary health institution that prides itself as a tertiary health facility with a state-of-the-art technology in a conducive and clean environment. It is the only hospital in the whole of Northern Nigeria that has the radionuclide scanning machine, hence, the suitability for this study that seeks to determine the evolution of RPS following febrile UTI. In 2016, the hospital had a pediatric outpatient attendance of 1575, with an average of 132 children per month [107].

Study Population and Eligibility Criteria

The intention is to enroll a minimum sample size of 500 consecutive febrile under-five children, whose parents or caregivers consent to the study's objectives. This sample size was expanded from the 260 derived from the Leslie Kish formula [108] at a standard normal deviation of 1.96 (corresponding to 0.5% CI), with a degree of accuracy set at 0.05 and using the prevalence of 21.4% for UTI among febrile under-five children in a similar study by Adedoyin et al [12].

However, to test the study's hypotheses, cases will be children with a confirmed RPS following a febrile UTI, and an equal

number of controls (age-, gender-, and ethnicity-matched children with a febrile UTI but without RPS) will be targeted from the sample size. The study would aim at having at least 50 cases and 50 controls.

The inclusion criteria are shown in [Textbox 1](#). The exclusion criteria are shown in [Textbox 2](#).

Recruitment

Four research assistants (RAs) will be employed for the purpose of recruiting the participants for this study. This will comprise 2 medical doctors and 2 nurses. The medical doctors shall be involved in conducting the dipstick urinalysis, automated urinalysis, anthropometrical measurements, and the collection of urine and blood samples from the recruited participants. The nurses will be in charge of obtaining informed consent, the administration of the questionnaire, and the follow-up of the recruited subjects to the radiological department of the National Hospital, Abuja. The RAs will be trained on the concept and objectives of the study and the quality and culture appropriateness of the study's questionnaire will be discussed with them. The proficiency of the RAs will be verified via role-playing. The study will use brochures, posters, flyers, newsletters, and family engagement to promote recruitment and retention within the study cohort. Parents or caregivers of febrile children coming to the EPU will be approached to be screened for enrollment. Furthermore, the study shall engage the services of a microbiologist, a radiologist, and a radionuclide physician. The microbiologist will be responsible for doing urine culture and interpretation, urine microscopy, and enhanced urinalysis. The radiologist shall be responsible for doing the RBUS and the MCUG. The radionuclide physician shall be responsible for the DMSA scanning for detecting APN and RPS.

Financial compensation will be made available for parents or caregivers who would have to bring their infants back to the National Hospital for MCUG at 14 days and for the DMSA scan at 6 months, following the treatment for the febrile UTI. To this end, the mobile telephone numbers of the consenting parents or caregivers of the children will be obtained for tracking after discharge from the hospital. In the same way, extra efforts will be made to obtain traceable home addresses of the study participants. Attrition would be minimized by ensuring that parents or caregivers fully understand this responsibility or expectation of study's protocol at the time of signing the consent forms.

Obtaining Ethical Access

Ethical approval for the study shall be obtained from the research and ethics committee of the National Hospital, Abuja and the institutional review board of the university that will be willing to supervise this proposal as a PhD thesis. A written informed consent (see [Multimedia Appendix 3](#)) shall be obtained from parents or caregivers of all children that will make the sample population of this study. The confidentiality and the privacy of research participants will be protected. The details of the informed consenting are as contained in Step 1 under the enrollment below. A rapid direct data sharing with the research community will be in accordance with the National Institutes of Health data sharing policy.

Textbox 1. Inclusion criteria.

- Consecutive febrile children (≥ 1 month-59 months of age) presenting at the emergency pediatric unit (EPU) of the National Hospital, Abuja, whose parents or caregivers give consent to the study.
- Fever is defined as axillary temperature $\geq 37.5^{\circ}\text{C}$ [109] using the mercury thermometer.
- Urinary tract infection (UTI) will be defined as a positive test result for pyuria by either microscopy (≥ 5 white blood cells per high-power field in uncentrifuged urine specimen) or dipstick test (positive leucocyte esterase test) and a positive growth on culture of at least 50,000 colony-forming unit (CFU) per mL of a single uropathogen in urine specimen obtained by catheterization or greater than 100,000 CFU per mL of a single uropathogen in clean-catch urine specimen or any uropathogen growth in urine obtained suprapubically [84].
- Renal parenchymal scarring (RPS) will be defined as a kidney with a decreased or an absent uptake in one or more areas, or relative function less than 45% on a dimercaptosuccinic acid (DMSA) scan done at 6 months following a confirmed febrile UTI.
- Parents or caregivers' ability to understand and comply with planned study protocols.
- Parents or caregivers' ability to provide informed consent before recruitment into the study.
- Parents or caregivers residing in study area and at least within 5 miles radius, for easy follow-up and to reduce the number that may be lost to follow-up.

Textbox 2. Exclusion criteria.

- Febrile under-five children who had taken antibiotics in the preceding 2 weeks.
- Children who have been treated for urinary tract infection (UTI) before.
- Children with neurological lesion causing bladder dysfunction or those with known stone disease
- Children with known congenital abnormalities of the kidney and the urinary tract (CAKUT, ie, vesicoureteral reflux, VUR; cystic kidney diseases; renal dysplasia; renal hypoplasia).
- Children with HIV or AIDS and those with sickle cell anemia, as these diseases may confound the finding of renal parenchymal scarring (RPS).
- Children with mixed ethnicity defined as having more than one ethnic ancestry in the biological parents and grandparents.
- Children who are already part of another ongoing research effort.
- Children whose parents or caregivers will refuse to give informed consent for participating in the study.
- Children whose parents or caregivers are institutionalized (eg, prisoner, nursing home residents, and prisons).

Step-by-Step Recruitment Process for the Study**Step 1: Enrollment**

The first step is to do screening to confirm study eligibility and provide participants with information about the study. A questionnaire (see [Multimedia Appendix 4](#) for the sample of the study's questionnaire) assessing eligibility will be completed, and contact information, including mobile phone numbers of the parents or caregivers, their relatives, or neighbors will be obtained. Traceable home addresses of the participants will also be obtained. Informed consent will then be obtained from the parents or caregivers of the prospective study's participants. Consenting will be done in the privacy of the consultation room (isolated from ambient noise and distractions) where the participant is being attended to. Consenting will be in simple understandable English. When necessary, translations into the participants' native language will be done for a better understanding. Before signing the informed consent, the details of the consent form shall be orally reviewed with the potential participant and answers to any questions that the participant has concerning participation in the study shall be given. The original signed consent form will be stored in the participant's study file, and a copy of the signed consent form will be given to the participant. Specifically, the following must be accomplished during the informed consent process:

1. The participant will be informed that participation in the study is *voluntary* and that refusal to participate will involve no penalty or loss of benefits or negative impact on their medical care.
2. The participant will be informed of the *purpose* of the study and that it involves *research*.
3. The participant will be informed of *any alternative procedures*, if applicable.
4. The participant will be informed of any foreseeable *risks*.
5. The participant will be informed of any *benefits* from the research.
6. An outline of safeguards to protect participant *confidentiality* will be included, as well as an indication of the participant's right to withdraw without penalty. This would be balanced with a discussion of the effects withdrawals have on the study and the responsibility a participant has, within limits, to continue in the study if he or she decides to enroll.
7. The participant will be informed *whom to contact* for information about research subjects' rights, information about the research study, and in the event of research-related injury.
8. The participant will be informed as to whether or not *compensation* is offered for participation in the study and/or in the event of a medical injury.

9. The participant will be informed that he or she will be notified of any significant changes in the protocol that might affect their willingness to continue in the study.
10. The informed consent form will be duly signed or thumb-printed and dated by the participant or witness before initiation of any study-related activity.

Step 2: Obtaining the Enrollees' Sociodemographic Data, Other Relevant Information, Biological Specimens, and Renal and Bladder Ultrasound Scanning

A well-structured questionnaire ([Multimedia Appendix 4](#)) will be used to capture information relating to sociodemographics and other relevant information that may confound the outcome (UTI). It will take approximately 30 to 45 min to complete the questionnaire. The information the questionnaire seeks to obtain shall include the following:

1. Sociodemographic data: age as at last birthday, gender, place of residence (urban or rural), ethnicity or tribe, and socioeconomic status of the household
2. Past medical history: prior use of antibiotics, past history of UTI, family history of recurrent UTI, family or subjects' history of congenital anomaly of the urogenital tract (ie, VUR), prior history of worm infestations, history of constipation, and history of breastfeeding in the first 6 postnatal months
3. Symptoms: jaundice, poor feeding, vomiting, diarrhea, irritability, strong smelling urine, abdominal pain, flank or back pain, irritability, dysuria, frequency, dribbling, poor stream, or straining to void
4. Signs: acutely ill-looking or not, fever (degree and duration before presentation), undernutrition as determined from anthropometric (height or length, weight, midarm circumference, occipitofrontal circumference) measurement, tenderness of the flank or costovertebral angle, suprapubic tenderness, abdominal tenderness, circumcision, signs of irritation on the external genitalia, pinworms, vaginitis, trauma, or sexual abuse
5. Comorbidity: malaria, sepsis, upper respiratory tract infection or otitis media, pneumonia, NS, viral exanthema, malignancies, etc

The following biological specimen will be collected from the enrolled child:

1. The urine sample will be collected as per the method relevant to the age of the child. Urine will be studied for culture and sensitivity and antimicrobial activity analysis. Furthermore, the urinalysis will be done by dipstick, urine microscopy, automated urinalysis, and enhanced urinalysis.
2. About 2 mL of blood will be collected using the sterile procedure for each child and sent for complete blood count, polymorphonuclear cell counts, ESR, CRP, PCT, TNF- α , IFN- γ , HIV, and hemoglobin genotypes.
3. Other laboratory work, including viral screening (hepatitis B or C), blood culture, stool microscopy, culture and sensitivity, cerebrospinal fluid culture and sensitivity, x-ray investigations, and joint fluid aspirate studies will be according to the diagnostic work-up for the particular child.
4. Additional 1.5 mL of blood shall be collected for APOL1 DNA analysis for all children with confirmed UTI.

RBUS scan will be done for all children with a confirmed UTI.

Step 3: A 14-Day Follow-Up of Children With Confirmed Urinary Tract Infection for Micturating Cystourethrogram

Any child with a confirmed febrile UTI as discussed previously will be subjected to MCUG at 14 days follow-up, *only if* the RBUS shows features of hydronephrosis, scarring, high-grade VUR, or obstructive uropathy. The MCUG would then confirm VUR and its grade. If it happens that the child has been discharged before this time, the parents or caregivers shall be contacted to bring the child for MCUG. Before this time point (2 weeks), RAs will be in constant contact with the parents or caregivers of discharged children via telephone calls and SMS text messages (short message service, SMS).

Step 4: A 6-Month Follow-Up of Children With Confirmed Urinary Tract Infection

All children with a confirmed UTI but without a VUR are expected to have a DMSA scan at 6 months of follow-up for evaluation of chronic RPS. Before this time point (6 months), the RAs will also be in constant contact with the parents or caregivers of discharged children via telephone calls and SMS text messages. The flowchart of the four steps is summarized in [Multimedia Appendix 5](#).

Laboratory Procedures and Measurements

Serum Analysis

A total of 3.5 mL will be collected from the recruited subjects in step 2. The blood collected will be allowed to clot and centrifuged to produce the serum for biochemical analysis that will include serum TNF- α , IFN- γ , PCT, and CRP. The WBC counts and the differentials (polymorphonuclear cells) will be measured using the automated hematological analyzer (SYSMEX automated hematology analyzer KX-21N, Sysmex Corporation, Kobe, Japan). Serum levels of TNF- α and IFN- γ will be assayed by ELISA (BD Biosciences, United States) according to the manufacturer's instructions. The TNF- α concentration will be calculated in the test samples on the basis of the curve produced by plotting the optical density values of the known standards (range: 7.5-500 pg/mL) on log-log graph paper.

The level of serum IFN- γ will also be detected with the IFN- γ ELISA kit. The detection limits of the kit for TNF- α and IFN- γ will be 2 and 1 pg/mL, respectively.

PCT will be measured with a quantitative immunoluminometric assay (LUMitest PCT, progressively replaced by PCT sensitive KRYPTOR, both from Brahms Diagnostica, Berlin, Germany), with a maximum interassay variation of approximately 0.3 ng/mL. CRP will be measured using the latex agglutination method and the automated method on Roche Integra 400 with an analytical goal of $\pm 10\%$.

DNA Analysis

This study will employ the new "Axiom Genome-Wide Pan-African Array Set" to perform the genome-wide genotyping for variants in the APOL1 gene rather than the limited candidates' SNPs (ie, rs73885319 and rs60910145 in G1 and rs71785313 in G2). DNA samples will be prepared and brought

to a concentration of 100 ng required per array in the *Axiom Genome-Wide Pan-African Array Set*. The manufacturer's protocol for Axiom 2.0 Assay Manual Workflow will be used for sample processing and preparation for genotyping. The Axiom genotyping array data will be analyzed by use of Affymetrix Power Tools to perform quality control analysis and sample and/or SNP filtering before the downstream analysis. The DNA analysis will be done at a reputable laboratory.

Urine Culture

The urine culture will be done within 1 hour of collection, employing the quantitative method as described by Guttman and Stokes [110]. Each uncentrifuged urine sample will be well mixed and inoculated onto plates of cystine lactose electrolyte deficient medium and blood agar as described by Urquhart and Gould [111] and incubated aerobically at 37°C for 24 hours after which the colonies will be counted with a colony counter.

The bacterial isolates will be identified based on colony morphology characteristics, Gram stain reaction, and biochemical tests using standard techniques [112]. Antibiotic sensitivity pattern of the isolates will be determined by the disc diffusion method in accordance with the National Committee for Clinical Laboratory Standards [113]. The discs will be placed on the agar surface and incubated for 24 hours. After incubation, the diameter of the zone of inhibition will be measured and compared with a zone diameter interpretative chart to determine the sensitivity of the isolates to the antibiotics.

When tests on the urine will not be performed within the first hour of urine collection, urine will be stored in the refrigerator (at 4°C) and will be tested within 4 hours of storage in the refrigerator [114]. Urine refrigerated will be kept at room temperature for 15 min before tests will be performed on them [114].

Dipstick Urine Analysis

The uncentrifuged urine sample will be used, and the procedure will follow a standard method. The analysis will specifically look for leukocyte esterase, nitrite, hematuria, and proteinuria.

Microscopic Urine Analysis

The microscopic analysis will take place after centrifuging of the urine and will follow the standard procedure [114]. The finding of >5 WBCs per HPF in a centrifuged urine specimen will be considered as pyuria. Bacteriuria is the finding of bacteria on urine microscopy.

Enhanced Urinalysis

Uncentrifuged urine will be drawn into a Neubauer hemocytometer via capillary action [115]. Pyuria will be assessed by counting WBCs on each side of the chamber, averaging the value and multiplying by 1.1 to obtain the number of WBCs per mm³. Two drops of uncentrifuged urine will be placed on a sterile slide within a standardized marked area of 1.5 cm diameter, air-dried, fixed, and Gram stained. Bacteriuria will be assessed as the average number of bacteria per 10 oil immersion fields; morphology and Gram-stained smear results would be reported.

Automated Urinalysis

Automated urinalysis [115] operates on the principle of flow cell digital image capture in combination with a trained neural network (Auto-Particle Recognition, APR software). Aspirated urine is hydrodynamically focused between two layers of suspending fluid (planar flow), forcing particles to orient in a single plane facing a microscope objective lens coupled to a digital camera. Five hundred fields of digital image are captured per specimen. APR software is programmed to recognize the size, shape, contrast, and texture of urine particles. APR classifies particles into 12 categories, including red blood cells, WBC, WBC clumps, hyaline casts, unclassified casts, squamous epithelial cells, nonsquamous epithelial cells, yeast, bacteria, unclassified crystals, mucus, and sperm. Representative images are then screened by a technician for accuracy and confirmed or adjusted accordingly. For this study, digital images will be stored for subsequent editing by a single experienced technician (DL). Dipstick results will be obtained by reflectance spectroscopy and included pH, specific gravity, nitrite, and leukocyte esterase. The automated WBC count is reported per HPF, and a conversion factor of 5.5 will be used to convert the automated WBC values reported per HPF to mm³.

Other Tests

Other investigations, including blood culture, joint aspirates for microbiology study, chest x-ray, stool microscopy culture, and sensitivity will be according to individual appropriateness.

Renal and Bladder Ultrasonography

RBUS will be requested for all bacteriologically confirmed cases of UTI while they are still on admission. All children will be examined in a warm room. Mothers will be requested to give water to the children to drink 1 to 1.5 hours before scanning. The abdominopelvic scan will be done using an Ultrasound SDD-3500 Plus, Japan 2005 scan machine with a 3-5 MHz curvilinear transducer. With the patient lying supine, the abdomen will be exposed, and gel will be applied. The transducer will be placed on the abdomen and gently moved laterally to the right and the left flanks from the midabdomen for the visualization of the right and the left kidney, respectively. The transducer will also be moved to the suprapubic region to localize the urinary bladder, especially when adequately distended with urine.

Voiding Cystourethrography

VCUG is after antibiotic therapy and will be done at 2 weeks for cases of confirmed UTI having hydronephrosis, scarring, high-grade VUR, or obstructive uropathy on RBUS. Children will be told to void (for those who can obey a command), after which, a preliminary coned down view of the bladder is taken. With the patient lying supine on the x-ray table and under aseptic technique, a lubricated catheter will be introduced into the bladder, and any residual urine will also be drained. A total of 150 mL of contrast medium (Urografin or Utravist) will be introduced into the urinary bladder until it is adequately distended. When the radiologist is convinced that the child will micturate or when the child shows the urge to micturate, the catheter will then be removed quickly. Spot films will then be taken during micturition. Films of the entire urethra and a

full-length view of the abdomen will also be taken to demonstrate any reflux into these organs.

Dimercaptosuccinic Acid Scan

The static renal scintigraphy will be done 2 to 4 hours after DMSA injection at a dose of 1 MBq/kg body weight (minimum 15 MBq). Planar images will be obtained by a high-resolution collimator in one posterior and two oblique projections with 300,000 counts in the posterior view. All data files will be evaluated by the consultant nuclear medicine specialist.

The maximum irradiation dose would be 2 millisieverts (1 millisievert from MCUG and 1 millisievert from DMSA scan [116])

Specimen Management

All specimens will be properly labeled and secured in a specimen bag with an accompanying laboratory request form. All specimens will be secured in a specimen carrier and transported to the study laboratory. All specimens will be delivered to the laboratory no longer than 3 hours after collection. Subject enrollment will occur only during weekdays and between 8.00 AM to 4 PM for logistic reasons. Specimens will be duly processed, and preliminary culture results will be made available to the researcher and the attending physician during the first 48 hours after enrollment and final results within 5 days. All clinical samples will be carefully labeled and coded using freezer-resistant labels. An electronic storage file will be developed to facilitate storage and retrieval of specimens.

- 2 mL of blood will be allowed to clot for 30 min, centrifuge for 20 min at 2400 rpm, and store at 4°C and ship with cold packs for TNF- α AND IFN- γ assay.
- 1.5 mL of blood, stored at 4°C and ship with cold packs for DNA analysis.
- Whenever there is a requirement to store sample at -20°C or -80°C, the freezer at the Professor Obaro's Research Laboratory of the International Foundation Against Infectious Disease in Nigeria (IFAIN) will be used.
- A database will be created for logging all stored samples.

Data Management

All participants will have a study identification to be used on study's questionnaire and biospecimens. Questionnaires will be kept without patients' identification information in a secured locked location as per the policies of Institutional Research and Ethics Board per site. All data will be checked for consistency, and outliers will be identified by examining empirical distributions of each outcome. All data will be entered into REDCap, a secured online tool.

Statistical Analysis

Statistical analysis will be done with SPSS version 21 (IBM Corp).

Statistical Analysis for Specific Aim 1

For numerical characteristics with symmetrical distribution, means and SD will be used as a measure of dispersion, whereas median and the interquartile range will be used to measure the central tendency for skewed numerical data. For categorical variables, proportions and percentage distribution would be

described. Age grouping (≥ 1 month-2 months, > 2 months-12 months, > 12 months-24 months, > 24 months- 59 months) will be done to take care of the known age-dependent risk of UTI [2]. Prevalence rates with 95% CIs will be calculated for UTI. Proportion distribution of UTI across the comorbidities will be described. The screening (ie, sensitivity, specificity, negative and positive predictive values) values of nitrite, leucocyte esterase, proteinuria, and hematuria on dipstick urinalysis will be compared with the urine culture. Furthermore, pyuria and bacteriuria identified on microscopic analysis and on enhanced urinalysis will be compared with bacteriologically confirmed UTI for sensitivity, specificity, and negative and positive predictive values. The dipstick urinalysis will be compared with the automated urinalysis in terms of screening values for UTI as confirmed by the urine culture. For children with a confirmed UTI, comparisons will be made between potential predictor variables (ie, sociodemographic variables, past medical history, symptoms and signs, and comorbidities) and UTI using chi-square test of proportions or, in the case of small samples, Fisher exact test. Predictors that attained significance at P value of .05 (except a priori predictors such as age and grade of fever, regardless of the P values) will be considered for multiple logistic regressions to evaluate the possibility of confounding in the relationship with UTI. For all analyses, P values less than .05 will be considered statistically significant.

Statistical Analysis for Specific Aim 2

The prevalence rates of children who developed RPS will be calculated. Cases shall be children who develop RPS consequent to febrile UTI and who also do not have VUR. Controls shall be children with confirmed UTI but who do not develop RPS. The risk of developing RPS across the age groups (≥ 1 month-2 months, > 2 months-12 months, > 12 months-24 months, > 24 months-59 months) will be determined. Proportion distribution of RPS in children with UTI will also be done across the various potential risk factors of RPS, including age at diagnosis of UTI, gender, delayed treatment (> 6 days of fever), peak of fever, laboratory indices of inflammation (total WBC count, ESR, IFN- γ , TNF α , PCT, and CRP concentration), the extent of renal parenchymal lesions, ethnicity (the major Nigerian ethnic groups of the Yorubas, the Ibos, the Fulanis, the Hausas, and others categorized as Others), and the presence of VUR. Ethnicity of the child will be that of his biological father and mother and the grandparents. Chi-square test of proportions or, in the case of small samples, Fisher exact test will be used to test the association between each of these risk factors and RPS. Predictors that attained significance at P value of .05 will be considered for multiple logistic regressions to evaluate the possibility of confounding in the relationship with RPS. For all analyses, P values less than .05 will be considered statistically significant.

Statistical Analysis for Specific Aim 3

The dependent variable is RPS and the independent variables will be the possession of either the G1 and/or the G2 APOL1 nephropathy risk variants. The possession of either the G1 and/or the G2 APOL1 will also be done among the cases defined by their ethnic groups of Yorubas, Ibos, Fulanis, Hausas, and Others. Ethnicity of the child will be that of his biological father

and mother and the grandparents. Chi-square test of proportions or, in the case of small samples, Fisher exact test will be used to test the association between the possession of either the G1 and/or the G2 APOL1 risk variants and RPS. The APOL1 gene alleles associated with RPS will be described. Comparisons will be made between potential predictor variables and RPS using chi-square test of proportions or, in the case of small samples, Fisher exact test. At the least, the following factors will be considered for inclusion in the prediction model: age groups, sex, ethnicity, APOL1 gene allele, measured temperature at the time of diagnosis, duration of fever before presentation, the organism isolated from culture (*E coli* vs others), results of renal ultrasonography (normal vs any abnormality), and levels of inflammatory markers (TNF- α and INF- γ , CRP, ESR, PCT, and polymorphonuclear cells). In most cases, potential predictors will be dichotomized into either “yes” or “no.” Predictors that attained significance at *P* value of .05 will be considered for multiple logistic regressions to evaluate the possibility of confounding in the relationship with RPS.

Statistical Analysis for Specific Aim 4

The outcome variable will be UTI, and the independent variables will be the various grades (I-V) of VUR. The effect of compounding with other significant risk factors (*P* value of .05) for UTI derivable from Specific Aim 1 above will also be determined using the multiple logistic regression analysis.

Statistical Analysis for Specific Aim 5

Comparisons will be made between clinical predictor variables (ie, age, gender, ethnicity, past medical history, symptoms and signs, and comorbidities) and RPS using chi-square test of proportions or, in the case of small samples, Fisher exact test. In most cases, potential predictors will be dichotomized into either “yes” or “no.” Predictors that attained significance at *P* value of .05 will be considered for multiple logistic regressions to evaluate the possibility of confounding in the relationship with RPS. For laboratory predictors, the sensitivity, specificity, and negative and positive predictive values of serum TNF- α , INF- γ , PCT, CRP, ESR, and polymorphonuclear cell count in

detecting RPS would be compared. For all analyses, *P* values less than .05 will be considered statistically significant.

Gene Analysis

All candidate gene analyses will be analyzed. Each of the SNPs to be examined will be analyzed individually with RPS. Logistic regression model will be used for RPS, and the likelihood ratio test for significance will be used. The overall test of genotypic association with two degrees of freedom and any statistical contrasts will be defined by three genetic models: dominant, additive, and recessive models, respectively (each with one degree of freedom), with and without adjustment for covariates. If the test of general association is significant, then three a priori genetic models will be explored, and the best genetic model will be selected without further adjustment for multiple comparisons. Multiple SNPs from each gene will be tested, and Bonferroni correction to account for multiple testing will be done. The effect size for each of the risk haplotypes will be tested using a generalized linear model defined depending on the outcome variable.

Table 1 is the summary of the statistical analyses of the primary and secondary outcomes of the study.

Power Calculations

The graphical representation of the power to detect association in the 500 minimum sample size populations can be seen in Multimedia Appendix 6.

For the proposed 500 minimum sample size, and assuming frequency of the exposure risk of haplotypes of APOL1 G2 (2 risk alleles) at 15% in the general population [117], the calculation indicates that the proposed sample size provides sufficient power ($\geq 80\%$) to detect significant association, if present.

Timeline of Study

Table 2 depicts the timeline of the research proposal that is expected to last for 3 years.

Table 1. Statistical analyses of the primary and secondary outcomes of the study.

Outcome	Definition	Variable	Analyses
Primary			
Urinary tract infection (UTI) among febrile children aged 1 month to 5 years	UTI will be defined as a positive test result for pyuria by either microscopy (≥ 5 white blood cells per high-power field in uncentrifuged urine specimen) or dipstick test (positive leucocyte esterase test) and a positive growth on culture of at least 50,000 colony-forming Unit per mL of a single uropathogen in urine specimen obtained by catheterization or greater than 100,000 CFU per mL of a single uropathogen in clean-catch urine specimen or any uropathogen growth in urine obtained suprapubically	Dichotomous (yes or no)	Prevalence ratios, odds ratio (OR), 95% CI
Secondary			
Renal parenchymal scarring among febrile children aged 1 month to 5 years with confirmed UTI	A kidney with decreased or absent uptake in one or more areas or relative function less than 45% on dimercaptosuccinic acid scan	Dichotomous (yes or no)	Prevalence ratio, OR, 95% CI, logistic regression

Table 2. Timeline of study

Activity	Year 1	Year 2	Year 3
Study year 1: 1-6 months			
Institutional review board approval	January to June		
Hiring and training of research assistants	January to June		
Engagement of microbiologist, radiologist, and radionuclide physician	January to June		
Study year 1: 6-12 months			
Project enrollment	July to December		
Shipping of samples for apolipoprotein L1 (APOL1) analysis	July to December		
Study year 2: 1-12 months			
Project enrollment		January to December	
Shipping of samples for APOL1 analysis		January to December	
Study year 3: 1-6 months			
Project enrollment			January to June
Shipping of samples for APOL1 analysis			January to June
Study year 3: 6-12 months			
Analysis of data			July to December
Writing reports and manuscript			July to December
Defense of PhD thesis			July to December

Results

Primary Outcome

The primary outcome measure is UTI in febrile children aged 1 month to 5 years.

Secondary Outcome

The secondary outcome measure is RPS among the children with confirmed UTI. The study will show for the first time the burden of RPS following a febrile UTI among Nigerian under-five children. It will also highlight if the risk of acquiring RPS is dependent on having APOL1 kidney disease risk variants among the children with confirmed febrile UTI.

Participant recruitment for this case-control cohort study will commence when the researcher gets a placement for a PhD study and after securing adequate funding grants for the study. The study is expected to last for at least 3 years.

Discussion

Principal Findings

This study will employ the new *Axiom Genome-Wide Pan-African Array Set* to perform the genome-wide genotyping for variants in the APOL1 gene rather than the limited candidates' SNPs (ie, rs73885319 and rs60910145 in G1 and rs71785313 in G2). The *Axiom Genome-Wide Pan-African Array Set* is currently the first array optimized for coverage of multiple African ancestry populations, and it maximizes coverage of common and rare variants in population of Yoruba, Luhya, and Maasi ancestry and admixed populations with West African ancestry. Its coverage of common and rare allele is

≥90% in Yoruba and ≥85% in Luhya and Maasi. The array includes over 2,000,000 SNPs selected from HapMap, 1000 Genomes, the Southern African Genomes Projects, the Sanger Center Cancer Gene Census, and the National Human Genome Research Institute Catalog of Published Genome-Wide Association Studies, and the SNPs include important disease and biological categories such as coding SNPs, pharmacogenomics genes, cardiovascular genes, major histocompatibility complex genes, and immune and inflammation pathway genes.

Limitations: Potential Pitfalls and Alternatives

A major concern is getting funds to execute a study of this nature. However, through application for grants, it is hoped that there would be light at the end of the tunnel.

There is also a concern that there may be an insufficient sample size of children with RPS that would serve as cases. Although this may impact on statistical significance of predictor variables in regression analyses, this limitation will be surmounted by extending the study period until a satisfactory number of 50 is attained.

The pitfall of possible attrition at 2 weeks and 6-month time points will be reduced by ensuring that only parents or caregivers who fully understand the study protocol and are willing to comply with it are recruited into the study in the first place. A modest monetary incentive would also be provided when parents or caregivers bring their children at these two time points. Traceable home addresses and mobile telephone numbers of the participants would be gotten, and close contact would be maintained by periodic telephone calls.

In Nigeria, as in many sub-Saharan African countries, political and economic instability can hamper longitudinal biomedical research via incessant strikes and erratic essential services such as electricity. The engagement of the researcher in other large-scale studies would enable him to have access to the uninterrupted electricity supply already put in place by the IFAIN. Biological specimens requiring refrigeration (including -80°C freezers) will be kept at the IFAIN laboratory service in Abuja, pending the appropriate time of shipment of such specimens.

All genetic data will be checked for consistency, and outliers will be examined. Genotypic error will be examined by

including blind replicates to assess assay reproducibility and the assessment of Hardy-Weinberg (H-W) proportion for each SNP. Reproducibility of the assay using replicate samples will be assessed using the kappa statistic. SNPs showing considerable discordance (kappa .9) will be discarded from subsequent analyses. Allele frequencies for each SNP will be computed and tested for departures from the H-W proportions. SNPs that persist out of H-W proportions after testing for genotyping error will be kept in the analyses as they may provide valuable insight into population ancestry, or signal a genome region for which the study sample is biased or is under selection pressure.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

The researcher's capacity to conduct this study.

[[PDF File \(Adobe PDF File\), 122KB - resprot_v7i6e156_app1.pdf](#)]

Multimedia Appendix 2

The conceptual framework of the study.

[[PDF File \(Adobe PDF File\), 163KB - resprot_v7i6e156_app2.pdf](#)]

Multimedia Appendix 3

The informed consent form.

[[PDF File \(Adobe PDF File\), 45KB - resprot_v7i6e156_app3.pdf](#)]

Multimedia Appendix 4

Questionnaire.

[[PDF File \(Adobe PDF File\), 63KB - resprot_v7i6e156_app4.pdf](#)]

Multimedia Appendix 5

The flowchart of the study's four steps.

[[PDF File \(Adobe PDF File\), 26KB - resprot_v7i6e156_app5.pdf](#)]

Multimedia Appendix 6

The power chart to show the strength of association.

[[PDF File \(Adobe PDF File\), 29KB - resprot_v7i6e156_app6.pdf](#)]

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Abbreviations

- ANG II:** angiotensin II
- APN:** acute pyelonephritis
- APOL1:** apolipoprotein L1
- CFU:** colony-forming unit
- CKD:** chronic kidney disease
- CRP:** C-reactive protein
- CXCL:** chemokine ligand
- DMSA:** dimercaptosuccinic acid
- EPU:** emergency pediatric unit
- ESR:** erythrocyte sedimentation rate
- ESKD:** end-stage kidney disease
- ESRD:** end-stage renal disease

FSGS: focal segmental glomerulosclerosis
HIVAN: HIV-associated nephropathy
IFAIN: International Foundation Against Infectious Diseases in Nigeria
IFN- γ : interferon- γ
IRF3: interferon regulatory factor 3
MCUG: micturating cystourethrogram
NS: nephrotic syndrome
PCT: procalcitonin
PRR: pattern recognition receptor
RA: research assistant
RBUS: renal and bladder ultrasound
RPS: renal parenchymal scarring
SNP: single nucleotide polymorphism
TGF- β : transforming growth factor β
TLR4: toll-like receptor 4
TNF- α : tumor necrosis factor-alpha
UTI: urinary tract infection
VEGF: vascular endothelial growth factor
VUR: vesicoureteral reflux
WBC: white blood cell

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Early Report

Implementation of a Cardiogenic Shock Team and Clinical Outcomes (INOVA-SHOCK Registry): Observational and Retrospective Study

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Abstract

Background: The development and implementation of a Cardiogenic Shock initiative focused on increased disease awareness, early multidisciplinary team activation, rapid initiation of mechanical circulatory support, and hemodynamic-guided management and improvement of outcomes in cardiogenic shock.

Objective: The objectives of this study are (1) to collect retrospective clinical outcomes for acute decompensated heart failure cardiogenic shock and acute myocardial infarction cardiogenic shock, and compare current versus historical survival rates and clinical outcomes; (2) to evaluate Inova Heart and Vascular Institute site specific outcomes before and after initiation of the Cardiogenic Shock team on January 1, 2017; (3) to compare outcomes related to early implementation of mechanical circulatory support and hemodynamic-guided management versus historical controls; (4) to assess survival to discharge rate in patients receiving intervention from the designated shock team and (5) create a clinical archive of Cardiogenic Shock patient characteristics for future analysis and the support of translational research studies.

Methods: This is an observational, retrospective, single center study. Retrospective and prospective data will be collected in patients treated at the Inova Heart and Vascular Institute with documented cardiogenic shock as a result of acute decompensated heart failure or acute myocardial infarction. This registry will include data from patients prior to and after the initiation of the multidisciplinary Cardiogenic Shock team on January 1, 2017. Clinical outcomes associated with early multidisciplinary team intervention will be analyzed. In the study group, all patients evaluated for documented cardiogenic shock (acute decompensated heart failure cardiogenic shock, acute myocardial infarction cardiogenic shock) treated at the Inova Heart and Vascular Institute by the Cardiogenic Shock team will be included. An additional historical Inova Heart and Vascular Institute control group will be analyzed as a comparator. Means with standard deviations will be reported for outcomes. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum will be reported. Reported differences will include standard errors and 95% CI.

Results: Preliminary data analysis for the year 2017 has been completed. Compared to a baseline 2016 survival rate of 47.0%, from 2017 to 2018, CS survival rates were increased to 57.9% (58/110) and 81.3% (81/140), respectively ($P=.01$ for both). Study data will continue to be collected until December 31, 2018.

Conclusions: The preliminary results of this study demonstrate that the INOVA SHOCK team approach to the treatment of Cardiogenic Shock with early team activation, rapid initiation of mechanical circulatory support, hemodynamic-guided management, and strict protocol adherence is associated with superior clinical outcomes: survival to discharge and overall survival when compared to 2015 and 2016 outcomes prior to Shock team initiation. What may limit the generalization of these results of this study to other populations are site specific; expertise of the team, strict algorithm adherence based on the INOVA SHOCK protocol, and staff commitment to timely team activation. Retrospective clinical outcomes (acute decompensated heart failure

cardiogenic shock, acute myocardial infarction cardiogenic shock) demonstrated an increase in current survival rates when compared to pre-Cardiogenic Shock team initiation, rapid team activation and diagnosis and timely utilization of mechanical circulatory support.

Trial Registration: ClinicalTrials.gov NCT03378739; <https://clinicaltrials.gov/ct2/show/NCT03378739> (Archived by WebCite at <http://www.webcitation.org/701vstDGd>)

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KEYWORDS

cardiogenic shock; mechanical circulatory support

Introduction

Background and Significance

Cardiogenic shock (CS) is the strongest predictor of mortality in patients who experience an acute myocardial infarction (AMI) or who suffer an episode of acute decompensated heart failure (ADHF). Observational studies have indicated that patient populations particularly at risk of developing cardiogenic shock post AMI or post an episode of ADHF include the elderly and patients with concurrent cardiovascular comorbidities [1]. Advances in efforts to provide early identification of CS, revascularization, and restored perfusion have positively affected mortality rates associated with myocardial infarction (MI) and have caused a dramatic fall in deaths associated with AMI in recent decades, while in the patients who develop CS post MI, mortality continues to be persistent and remains as high as 50% [2].

CS, also known as “pump failure” is precipitated by a profound reduction in cardiac output which results in tissue hypoperfusion secondary to a deficit of circulating blood, this lack of perfusion results in increasingly poor clinical outcomes [2,3,4]. Also defined as complete circulatory collapse, CS is characterized by shock occurring after a primary cardiac pathology in which cardiac output has been compromised. It involves refractory hypotension and tissue hypoperfusion secondary to heart failure after correction of preload and the culprit precipitating arrhythmia [2]. CS is representative of a diverse and complex clinical presentation which is the challenge of identification and management of this calamity. The onset of CS can be acute or progressive, as the ischemia representative of CS may develop from an acute, large, primary MI or can occur as a delayed extension of an original MI [2]. CS can occur acutely in patients with no prior history of cardiac disease, or progressively in patients with chronic heart failure [4]. The most common etiology of acute CS is the incidence of an acute coronary syndrome (ACS), specifically ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) which collectively has been reported to account for nearly 80% of cardiogenic shock cases [4]. Patients that develop CS post NSTEMI tend to develop dormant CS and are older with more complex cardiac comorbidities [2]. CS is the strongest predictor of mortality post MI. This is thought to result from both ischemic and mechanical complications. Mechanical complications of MI that contribute to CS include: acute mitral regurgitation secondary to rupture of the papillary muscle, rupture of the ventricular septal wall, or tearing of the ventricular wall [4]. CS can also arise from non-ACS causes

such as cardiac abnormality (primary, valvular, electrical, or pericardial), decompensated valvular disease, acute myocarditis, hypertrophic cardiomyopathy with aortic obstruction, cardiac tamponade, arrhythmia, traumatic injury to the chest (myocardium), post cardiectomy secondary to coronary artery bypass graft surgery, and progression of congenital lesions [4].

A designated, multidisciplinary shock team is critical in the assessment, implementation, and management of the CS patient. The collaborative efforts of a team which includes a cardiologist specializing in heart failure, a cardiothoracic surgeon, cardiac interventionalist, and an intensive care unit (ICU) intensivist working to manage the time-dependent clinical scenario will maximize outcomes related to CS [5]. The Cardiogenic Shock team at the Inova Heart and Vascular Institute (IHVI) is comprised of four clinical disciplines: Interventional Cardiology, Acute Heart Failure, Cardiac Surgery, and Critical Care. Their respective roles in the diagnosis, treatment and management of cardiogenic shock are highly specific yet profoundly collaborative. Interventional cardiology is at the vanguard of treatment and is usually the first point of contact. This group assists with mechanical circulatory assist device insertion and management both on hospital admission and throughout hospitalization. They also manage device weaning and escalation of support. The acute heart failure physician specialist helps to determine a patient's candidacy for temporary and durable mechanical support. The role of the cardiac surgeon is to assist with and evaluate a patient's candidacy for surgical support services. Finally, the critical care physician is the team quarterback and the central player in identifying the appropriate parties for emergency consultation as well as the advancement and management of the cardiogenic shock patient's day-to-day care during hospitalization. IHVI CS team goals can be identified as follows: rapid identification of CS as well as its etiology, maximization of survival through the utilization of mechanical circulatory support (intraortic balloon pump; Impella, percutaneous microaxial flow pump; Tandem Heart, percutaneous left ventricular assist device; peripheral extracorporeal membrane oxygenation [ECMO]; central ECMO; temporary vascular assist device; permanent vascular assist device; or transplant) as well as supportive therapies, and the development and implementation of a hemodynamic support plan with mechanical devices in the event of refractory CS [5]. Team-based interventions are crucial in critical illness as in the case of a “code team” (mandated by the Joint Commission on Accreditation of Healthcare Organizations) for the in-house management of cardiac arrest and a rapid response team for decompensating medical surgical patients. CS is similar to these

clinical clusters of symptoms and requires the early identification and specific expertise of many disciplines in order to manage this complex condition. The high mortality rate of CS patients can be tempered through early revascularization and the activation and utilization of a multidisciplinary shock team. The time sensitive nature of CS or the dictum “time to support” [6], with both percutaneous and surgical interventions, requires the activation of a multidisciplinary Shock team in order to manage circulatory collapse and the ensuing end organ dysfunction [6] or failure through prompt response and management of any changes in the patient’s condition in addition to early diagnosis.

A review of relevant literature identifies the benefit and recommends the implementation of a multidisciplinary shock team to improve outcomes in patients in danger of imminent circulatory collapse. Proposed recommendations are wide in scope yet highly specialized with respect to the requirements of this patient population. CS associated with acute MI or acute decompensated heart failure should be closely monitored for progression to decompensation and end organ failure. CS should be suspected and investigated post cardiac arrest due to the significant association between the two conditions by a multidisciplinary shock team [7]. Recommended personnel include a multidisciplinary oversight panel as well as experienced medical teams at a given site [7]. Medical, interventional cardiology, anesthesia, thoracic and vascular surgery, intensive care, and radiology [7] must be available to manage CS in a timely manner. The two strongest priorities in CS are hemodynamic stabilization and the rapid reversal of the low output state to maintain end organ perfusion and rapid coronary reperfusion, although not necessarily in that order, are optimally managed by a CS team [8,9]. Rehospitalization and death are most prevalent in the early discharge period [10]. These readmissions are frequently associated with volume overload as opposed to late readmissions which are associated with the natural trajectory of the syndrome for example cardiac remodeling [10]. This identifies the early discharge period as one where the patient is particularly vulnerable and the careful coordination of the multidisciplinary team as well as the transitional team are implemented to ensure that the care is patient-centered, as well as proactive in protection against recurrence of CS [10]. Activation of a coordinated cardiogenic shock team and early outcome specific therapy in a timely and synchronized manner ensures proper allocation of resources and is associated with increased survival in cardiogenic shock [11]. Successful device selection to support heart rate (HR) in underlying CS etiologies is enhanced by a multidisciplinary team approach including; heart failure specialists, interventional cardiologists, and cardiothoracic surgeons, with patients’ preferences accommodated in a timely manner [12].

The implementation and utilization of a designated CS at the IHVI is an effective strategy to mitigate the consequences of cardiogenic shock. The IHVI CS team, founded in 2017, is mobilized for and directed to five goals: (1) the rapid identification of shock through early activation of the CS team and rapid collaborative decision making, (2) early right heart catheterization to facilitate invasive hemodynamic therapy tailored to the patients’ unique presentation, (3) the accelerated

initiation of mechanical circulatory support, (4) minimization of vasopressor and inotropic support, and (5) meaningful recovery and survival of the patient [13]. Bi-weekly action and outcomes review are employed to track efficient methodology with the intention of eradicating significant preventable morbidity and death from CS [13]. Utilizing the best and most recent evidence and best practices, a comprehensive care pathway was developed. A six-month training process was focused on individual and team management of the aforementioned five goals, training and rehearsals were implemented to ensure the seamless execution of the adopted algorithms [13]. Prior to implementation of the Cardiogenic Shock team at the IHVI, 30-day survival was approximately 47%, assuming an alpha level of 0.5, two sided. We expect the implementation of an IHVI Shock algorithm to increase 30-day survival by 15%. Thus, 200 subjects in each group provide at least 80% power to detect a statistically significant increase in 30-day survival from 47%.

We propose to study the outcomes associated with CS patients who have been managed by the CS team at the IHVI in order to ascertain the effects on outcome and survival rate. Positive effects in outcomes and survival will indicate a positive correlation between meaningful survival and management by a multidisciplinary shock team. The database compiled from these outcomes will also serve as a clinical archive of distinctive patient characteristics and outcomes to support future evaluation and translational research. The benefit of CS management to patients is a decrease in disability and mortality post CS episode.

Specific Aims

The specific aims of this study are as follows: (1) to collect retrospective clinical outcomes related to acute decompensated heart failure cardiogenic shock, acute myocardial infarction cardiogenic shock and compare current versus historical survival rates; (2) to collect Inova Heart and Vascular Institute (IHVI) site specific outcomes before and after initiation of the Cardiogenic Shock team on January 1, 2017; (3) outcomes related to implementation of mechanical circulatory support versus no circulatory intervention and type of intervention (ECMO versus intracorporeal axial-flow [Impella]); and (4) to assess survival at 3 time points.

Hypothesis

We hypothesize that implementation of a Cardiogenic Shock initiative with early team activation, rapid initiation of mechanical circulatory support, hemodynamic-guided management, and strict protocol adherence will be associated with superior clinical outcomes at three time points: survival to discharge and overall survival, compared to 2015 and 2016 outcomes prior to shock team initiation.

Methods

Study Design and Subject Selection

Study Type

This is a retrospective and prospective, observational study. The Investigators acknowledge that a possible limitation of measuring and comparing the treatment effect of the team-based

approach with historical controls not exposed to team intervention may present selection bias due to the change in treatment paradigm, potential loss of blinding, lack of true point estimates, and increased risk of type I error.

Setting or Location

Outpatient or inpatient chart review utilizing EPIC, the electronic medical record utilized by the Inova Health System (HIS) for patients admitted to Inova Fairfax Medical Campus. EPIC review will occur at the Center for Thrombosis Research and Drug Development Center: 3300 Gallows Road, Inova Heart and Vascular Institute 3rd Floor, Fairfax, VA 22102.

Duration of Study

Chart review in EPIC will occur over a one-year period.

Number of Subjects

Our goal is to include approximately 200 patients before and 200 patients after initiation of Shock team. The study group will consist of a retrospective review of all patients receiving Shock Team intervention after diagnosis with acute decompensated heart failure cardiogenic shock, or acute myocardial infarction cardiogenic shock, from January 1, 2017 until Institutional Review Board (IRB) filing of protocol. A second group will consist of current patients receiving shock team intervention.

Study Population

Gender of Subjects

There are no gender-based enrollment restrictions. Subjects will include a distribution based on the demographics of the Northern Virginia population.

Age of Subjects

Anyone 18 years or older who underwent CS team intervention for acute decompensated heart failure cardiogenic shock, acute myocardial infarction cardiogenic shock will be included.

Racial and Ethnic Origin

There are no race-based enrollment restrictions. Subjects will include a distribution based on the demographics of the Northern Virginia population.

Vulnerable Populations

No vulnerable populations will be enrolled in this study.

Recruitment

Preliminary chart review in EPIC will be performed on all patients in our practice and those who have a previously undergone Cardiogenic Shock team intervention for acute decompensated heart failure cardiogenic shock, or acute myocardial infarction cardiogenic shock. No recruitment process will be necessary to obtain information.

Inclusion Criteria

Patients at the IHVI with documented Cardiogenic Shock team intervention for acute decompensated heart failure cardiogenic shock, or acute myocardial infarction cardiogenic shock.

Specific criteria for the diagnosis of cardiogenic shock is defined by hemodynamic parameters—systolic blood pressure <90 mm

Hg, cardiac index <1.8 L/min/m² without pharmacologic support (or >2.2 L/min/m² with support), left ventricular end-diastolic pressure >18 mm Hg or right ventricular end-diastolic pressure >10-15 mm Hg or pulmonary capillary wedge pressure >15 mm Hg—and clinical signs and symptoms of hypoperfusion, such as cool extremities, decreased urine output, and altered mental status.

Enrollment criteria are specific to patients treated at the IHVI for documented cardiogenic shock with activation of the IHVI Cardiogenic Shock team. Cardiogenic shock will have preceded acute decompensated heart failure or acute myocardial infarction etiologies. Patients will include those transferred from offsite hospitals as well as inpatients at the IHVI.

Exclusion Criteria

Patients under the age of 18 will be excluded.

Patients assessed to be comorbid (eg, life expectancy less than 6 months) were not deemed to be suitable candidates for temporary mechanical support or long-term, durable mechanical circulatory support and were excluded in principle from data abstraction

Research Database Participation Eligibility

Participant Eligibility Criteria

Any patient with cardiogenic shock, whether inpatient or transferred from another facility, treated at the Inova Heart and Vascular Institute. This includes adults with and without decision making capacity over the age of 18 years old.

Informed Consent

Informed consent is waived for the purpose of this research database. The procedural risk involved in this protocol meets the definition of minimal risk as set forth in 45 CFR 46.102 (i) “Minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” Participation in this protocol requires evaluation of medical data from patients who have experienced CS that is mined directly from the participant’s medical record.

Registry Data

The primary investigator will designate the data points to be included in the database in order to assess the efficiency of procedures and protocols in the treatment of CS at the IHVI as administered by the Shock team, to identify relationships between treatment and negative morbidity and mortality outcomes, and to monitor and improve quality of care delivered.

In addition to the defined data collected, additional participant data may be collected as needed for a specific study. This additional data would be contained in the participant’s medical records. Examples of this additional data that may be requested for a related additional study would be more detailed clinical data at the time of diagnosis or more detailed disease status data while experiencing cardiogenic shock. In no case will the participant be contacted in order to obtain additional data.

Collaboration With Other Registries

To facilitate both national and international research efforts in cardiogenic shock patient's collaborative studies may occur with other institutions outside of Inova. Detailed patient-level data obtained through the cardiogenic shock database can facilitate hypothesis-driven clinical studies. The information in the database will not only be utilized to drive internal investigator-driven projects but also be used to foster collaborative studies with institutions outside of INOVA. For any collaborative studies with outside institutions, a data use agreement will be in place. Dataset exporting will be restricted to the database manager and the primary investigator. Only a limited data set will be provided which includes dates to help identify clinical events. No other protected health information will be such as name, contact information, medical record identification number nor any other patient-specific identifiers will be provided to these collaborative partners. In addition, collaborative studies using the cardiogenic shock database will not be approved unless authorized by the principal investigator alone and the aforementioned data use agreement has been executed.

Data Confidentiality

Access to all information in the Cardiogenic Shock Research Database is securely controlled utilizing passwords and logins at multiple levels. Access to the research data base is limited to relevant IRB approved study team members and to employees with specific job responsibilities related to the database.

Registry participants are assigned a unique identification (UID) number when they are enrolled into the cardiogenic shock database. All protected health information (PHI) will be fully de-identified. The UID contains no identifying information. This UID is utilized to track all participant information in the research database. Protected health information is defined as:

1. Name
2. Geographical subdivisions smaller than State
3. Telephone number
4. Fax number
5. Electronic mail addresses
6. Social security numbers
7. Medical record numbers
8. Health plan beneficiary numbers
9. Account numbers
10. City, state, and country

Or any other specific identifying information will be collected at the time the unique identification number is assigned to ensure that the participant has not been previously registered. Identifying data will be stored in a secure database separate from the research database. This protected information will not be included in data sets used for analysis. The unique identification number will have no identifying information within it. This number will be used to track all information about the participant in the research database.

The identity of the database participants will be kept confidential at all times. All research staff at INOVA will maintain up-to-date training in protection of human subjects. This training is received through the Collaborative IRB Training Initiative

program. This is a Web-based training program offered through the University of Miami.

Endpoints or Outcome Measurements

Primary Outcomes

The primary outcomes of this study are to create an archive of retrospective clinical outcomes (acute decompensated heart failure cardiogenic shock, or acute myocardial infarction cardiogenic shock) and compare current versus historical survival rates and to evaluate all-cause mortality at hospital discharge.

Secondary Outcomes

Analysis of mortality by subgroup (age, sex, initial etiology, time to presentation, time to treatment, use of mechanical circulatory support, Incidence of major adverse cardiac and cerebrovascular events, and preservation of left ventricular function.

Statistical Considerations and Data Analysis

Sample Size

We are estimating 300-400 patients will be included in this analysis. This size is based on prior smaller studies.

Method of Data Analysis

Data will be collected from a chart review and recorded in a database spreadsheet. Statistical analysis will be performed to calculate data collected in this study. Results will be reported using summary tables and will be displayed for each treatment arm. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum will be presented. Reported differences will include standard errors and 95% CI.

Data Storage

Data Management

Designated study site staff will directly query EPIC and retrieve a set of defined data fields that can be directly integrated into INOVA's clinical or translational research database, REDCap. Specific forms will be used for each component of the subject's progress. The forms and data dictionary will be available online for all individuals who perform data entry. Research personnel, trained on data definitions will perform logical data checks to assess data quality. Suspect data entries will be flagged for review and confirmed by the investigative team at each site.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996. Privacy and confidentiality of all patients enrolled will be maintained. Steps will be taken to "de-identify" participants from their personal health information (PHI) by assigning each patient a PIN number that will not be linked to any specific PHI. The "key" linking the PIN to the patient's PHI will be maintained separately from the collected data and will be stored on a protected data file on a secure internet server requiring password login.

Records Retention

The investigator will maintain records in accordance with ICH Guidelines. Essential records will be stored for no longer than 3 years after the study is formally discontinued and then destroyed. Paper records will be shredded and recycled. Records stored on a computer hard drive will be erased using a commercial software application designed to remove all data from the storage device.

Human Subjects Protection (Risks, Benefits, and Alternatives)

Risks

There are no anticipated significant risks in this study. Potential loss of confidentiality will be minimized by shielding the participants by unlinking his or her identity from his or her personal health information

Benefits

There are no direct benefits to the patient.

Confidentiality

The Principal Investigator and Coinvestigators will be ultimately responsible for assuring the security of all computer systems to minimize risk to participants. The participant's identifiable private information will be handled, managed, and disseminated in a method which places confidentiality as the highest priority. Individuals who will have access to the data will need to be clearly delineated. The data will be stored in a Health Insurance Portability and Accountability Act of 1996 (HIPPA) compliant database, shared only with individuals who are participating in the study, and will be stored for no longer than 3 years and then eventually destroyed.

Subject Compensation

Costs and Payment

There are no costs to participate in the study. There will be no payment for participation in this study.

Adverse Event Reporting

There are no potential adverse events for participation in this study.

Results

Preliminary data analysis for the year 2017 has been completed. Compared to a baseline 2016 survival rate of 47.0%, from 2017 to 2018, CS survival rates were increased to 57.9% (81/140) and 81.3% (26/32), respectively ($P=.01$ for both). Survival in acute MI with CS increased from 52.6% (30/57) to 75.0% (12/16) and in acute decompensated HF from 61.4% (51/83) to 87.5% (14/16). For 2017, CS threshold markers at 12 hours (lactate<3.0 mg/dL, CPO>.6 W, PAPI>1.0) overall survival was 80% (72/90), 93.6% (73/78) and 74% (71/96), respectively. For 2018, CS threshold markers at 12 hours (lactate<3.0 mg/dL, CPO>.6 W, PAPI>1.0), overall survival was 92.3% (24/36), 92% (23/25) and 85.2% (23/27), respectively. Use of RHC was associated with 14% greater survival. Decreases of 5 and 10 hours in the time to implement MCS were associated with increased survival 53.6% and 135.8%, respectively. Age was associated with survival; patient's ≥ 75 years old had higher risk of death (odds ratio 3.43, 95% CI 1.20-9.78).

Discussion

Retrospective clinical outcomes (acute decompensated heart failure cardiogenic shock, acute myocardial infarction cardiogenic shock) demonstrated an increase in current survival rates when compared to pre-Cardiogenic Shock team initiation. IHVI site specific positive outcomes far exceeded the national average. Patients who had mechanical circulatory support did significantly better when the patient was younger than 75 years old at the time of intervention and when the mechanical circulatory support was initiated within five hours of the patients' arrival at the IHVI. Yet to be analyzed is the significance of the type of intervention ECMO versus intracorporeal axial-flow (Impella).

Acknowledgments

There is no external funding for this study. INOVA Health System network computers will be used to perform an Epic chart review and enter data into a HIPPA compliant database.

Conflicts of Interest

AT is a consultant for Abiomed Inc.

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Abbreviations

ACS: acute coronary syndrome
ADHF: acute decompensated heart failure
AMI: acute myocardial infarction
CS: cardiogenic shock
CPO: cardiac power output
ECMO: extracorporeal membrane oxygenation
HIPPA: Health Insurance Portability and Accountability Act
ICU: intensive care unit
IHVI: Inova Heart and Vascular Institute
MI: myocardial infarction
NSTEMI: non-ST-segment elevation myocardial infarction
PHI: personal health information
RHC: right heart catheterization
STEMI: ST-segment elevation myocardial infarction
UID: unique identification

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Original Paper

A Digital Decision Support Tool to Enhance Decisional Capacity for Clinical Trial Consent: Design and Development

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Abstract

Background: Challenges in the clinical and research consent process indicate the need to develop tailored, supportive interventions for all individuals, especially those with limited decisional capacity. We developed a tool to enhance shared decision making and the decisional capacity for individuals with fragile X syndrome engaged in the informed consent process for a clinical trial.

Objective: We describe the design and development process of a tablet-based decision support tool.

Methods: Our development process for the decision support tool employed a user-centered, feature-driven design approach. We began with an environmental scan to catalog relevant mobile apps, and we conducted interviews with people with a diagnosis of fragile X syndrome and clinicians at fragile X syndrome clinics. To develop content for the decision support tool, we extracted key concepts and elements from a real clinical trial consent form and rewrote it using plain-language principles.

Results: We used iterative testing to continuously evaluate and revise the decision support tool content. The tool was finalized in 2016 and contained a series of vignettes, quiz questions, and a sorting activity. A randomized controlled trial was then conducted to compare the efficacy of the decision support tool with a standard verbal presentation of material that mimicked typical informed consent practice.

Conclusions: The informed consent process is primed to leverage digital health resources that promote increased understanding and engagement of research participants in the consent and research process. The process and experiences we describe may provide a model for other digital health design and development initiatives seeking to create more interactive and accessible decision support resources.

Trial Registration: ClinicalTrials.gov NCT02465931; <https://www.clinicaltrials.gov/ct2/show/NCT02465931> (Archived by WebCite at <http://www.webcitation.org/6zx2KY9YW>)

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KEYWORDS

decision support; informed consent; digital health; intellectual disability; fragile X syndrome; telemedicine

Introduction

Digital Health and Decision Support

Digital technologies can serve as a communication bridge between patients, caregivers, and health care providers, making information available to users when and where they need it, and allowing users to better communicate their needs and preferences. For those with intellectual and developmental disabilities, technological advances can be used to support daily living skills, enhance cognition, and support communication. Further, multimedia formats for information delivery—including interactive, computer-based interventions—may contribute to greater patient understanding of complex information when compared with traditional formats [1-4] and are gaining in popularity [5].

Electronic informed consent strategies use electronic media (such as websites, video, or audio) to convey study information and obtain the participant's consent [5]. Researchers are beginning to see the potential value of electronic informed consent methods as opposed to traditional paper-based methods.

Prospective research participants sometimes struggle to comprehend informed consent standards and regulations [6]. One such challenge is a lack of general understanding of the research and important concepts [1,7]. Participants also struggle to understand the potential risks and benefits of research [7], and to understand their rights, the treatment they may receive [7], and the purpose of the research for which they are being asked to provide their consent [8,9]. Informed consent documents and informational materials for patients focus more on meeting minimal ethical requirements than facilitating the decision-making process [10]. Audiovisual interventions may have the potential to provide benefits to the informed consent process by improving participant understanding and satisfaction [11].

Overview of Fragile X Syndrome

Fragile X syndrome (FXS) is the leading inherited type of intellectual disability. Males with a diagnosis of FXS typically have impairment ranging from mild to severe; females are generally less impaired [12]. This wide range of cognitive skills among those with FXS can result in variable decisional capacity and the ability to make choices [13].

To date, most research on individuals with FXS has been noninvasive, limited to parent surveys and secondary assessment of clinical data [13,14]. Studies such as these typically involve straightforward consent or assent processes or parental consent. However, with advances in understanding the underlying science of FXS, the number of clinical trials available for individuals with FXS has increased [13,15]. Decisions related to enrollment in treatment trials are now more complex than in the past; thus, researchers are compelled to consider how best to support decision making for individuals who present with a range of decisional capacity. Recent technological advances in digital health have the potential to dramatically change the consenting process for those with FXS.

Decision Making and Fragile X Syndrome

The knowledge base surrounding the decisional capacity of those with intellectual disability and FXS is inadequate, and reviews concluded that the literature is limited in both scope and focus [14,16]. The few studies that examined ways to support individuals with intellectual disability in the informed consent process found that the presentation of information is important, given that language skills, memory, and previous decision making all have an impact on the ability to consent [16]. Due to the wide range in decisional capacity, those with intellectual disability can participate in the consent process, but many authors encourage that participation should be determined and supported on an individual case-by-case basis [13,16,17]. The use of digital decision support tools can potentially improve the understanding of clinical trial consent for those with FXS. The purpose of this paper is to describe the design and development process of a tablet-based decision support tool to enhance shared decision making and decisional capacity for those with FXS participating in the informed consent process.

Methods

Design Process

The user-centered design process outlines the design and development life cycle focused on gaining a deep understanding of a system's end users. A variety of user-centered design guidelines are available to inform the development of digital technologies. For example, the international standard 9241-210:2010 [18] provides the requirements and recommendations for human-centered design principles to guide the development of computer-based interactive systems. Several US federal resources to support implementation and management of user-centered design are freely available from the United States Digital Service [19], 18F [20], and usability.gov [21]. Our team leveraged these resources to develop a tablet-based decision support tool. Figure 1 outlines the methodology our project team used to identify and develop content for the tool.

Environmental Scan

To begin, our team conducted an environmental scan to catalog available tablet-based apps that focus on health care or were designed for individuals with intellectual and developmental disabilities. Our goal was to evaluate the apps based on user-centered design principles and determine what features we needed to include when developing the tool. Study staff purchased an iPad (Apple Inc, Cupertino, CA, USA) and identified 31 apps (see [Multimedia Appendix 1](#)) categorized as follows: (1) communication apps (n=10), (2) educational and social skills apps (n=8), (3) decision support apps (n=7), (4) clinical trial apps (n=3), and (5) behavior modification apps (n=3). Based on our review, we formulated recommendations for key features, outlined in [Table 1](#). Although the recommendations do not encompass all considerations necessary for tool development, they provide a well-rounded initial assessment of features either that are currently used by or with individuals of our target population, or that need to be developed and enhanced to address inequities for a successful informed consent decision support tool.

Figure 1. Methodology for decision support tool content development.



Table 1. Recommended key features of apps.

Decision support tool feature	Feature description
Apply clear communication and plain-language principles	The tool should reflect clear communication principles (eg, avoid jargon, use a low reading level) and be easy to understand.
Ensure appropriateness to sensitivities	Content and presentation elements need to be respectful of particular sensitivities common among individuals with fragile X syndrome (eg, heightened sensitivity to light, color, and sound).
Combine animation and real-life images	The combination of animation and real-life images provides engagement while grounding concepts in the real world and provides tangible orientation to relevant scenarios (eg, a clinic waiting room).
Enable customization	Customization of the content and delivery should be enabled to ensure accessibility to a broader audience.
Incorporate active learning	Active learning principles should be incorporated to facilitate greater engagement and integration of the information.
Assess comprehension	Existing methods (eg, the “teach back” method) should be incorporated or new ways should be developed to assess a user’s comprehension of information received to gauge the effectiveness of the tool.
Support decision making	Simple decision support tools should be offered to facilitate reasoning about a decision (eg, a pro/con list) and assessment of preference (eg, importance of factors) related to that decision.

Interviews With the Target Population

In the second step to inform the appropriate features and functionality for the decision support tool, we conducted 6 in-person observation-based interviews with individuals with a diagnosis of FXS. This was a convenience sample of participants identified through a larger study on health care decision making among individual with FXS; 5 participants were male and their average age was 22.3 years (range 16-28 years). Participants were given an iPad and rated on their engagement and performance of simple skills, advanced skills, and exploration skills interacting with specific apps. Overall, all participants interacted with the assessment apps and were most engaged with exploring app hotspots that involved avatars or narration, and least engaged with simplistic app features. Results from these interviews will be published at a later date.

Interviews With Clinicians

To establish a better understanding of the context within which the decision support tool would be used, we conducted 3 in-depth interviews with clinician stakeholders who had taken

participants with FXS through the consent process for clinical trials. This was a convenience sample of clinicians or physician scientists who were known members of our project team and willing to serve as consultants, and to provide feedback on the content creation, as well as the design and development efforts throughout the life cycle of the project. From the interviews, it was unclear whether there is a standard or maximum reading level for consent forms. One FXS clinical trial research manager stated that their consent forms were written for an eighth-grade reading level, and the other 2 clinicians noted that their forms include simple questions (possibly at a second- or third-grade reading level) to prompt a yes-or-no response from the patient. It was also the consensus that most individuals with FXS don’t understand much of the information presented to them; however, they are able to understand that they will be taking a new medication, and they are able to understand the risks and benefits of that new medication. Although none of the clinicians regularly used tablets as part of the informed consent process, one clinician emphasized that keeping the participant happy and engaged is the greatest challenge, and they welcomed anything to make the process easier.

Table 2. Sample decision support tool content mapping.

Institutional review board element	Real clinical trial consent	Hypothetical clinical trial consent	Decision support tool content
Description of risks or discomforts to subject.	Risks are possible side (adverse) effects from the study drug, other drugs, taking the blood pressure or taking blood.	The new medication is generally considered to be very safe, but one purpose of the study is to determine whether any serious side effects occur. The most common side effects expected are fatigue and a mild headache.	You might not like some parts of the study. If you get the real pills, you might feel a little sick or tired. You also might not like getting your blood drawn.
Description of voluntary compensation and treatment if the subject is injured related to the research. Applicable for research posing greater than minimal risks.	Each study subject will receive US \$200 per study visit when you have to stay overnight and US \$120 for other visits to the study center, to compensate for your time.	US \$25 will be given for each study visit and US \$10 for each phone call.	You will get US \$25 after each visit. Your name and information about you will be kept private.

Content Development

Content development began with a review of informed consent forms from previously conducted FXS clinical trials. Although the tool focused on a hypothetical trial, we used the actual consent forms as a guide to extract key concepts and elements that would also be needed in our tool (eg, randomization, blinding, and use of a placebo, as well as concepts that anecdotally are difficult to comprehend and typically explained with medical terminology and jargon). We rewrote these concepts and elements using plain-language principles and incorporating other recommendations we identified in the environmental scan. We used a table to map institutional review board requirements and the clinical trial consent content with language in the decision support tool to ensure that we addressed all mandatory elements of informed consent disclosure. [Table 2](#) shows a sample of how these elements were mapped. We consulted members of the institutional review board of RTI International, Research Triangle Park, NC, USA, to validate this process.

To aid in the development of closed-ended quiz questions for the tool, we adapted the MacArthur Competence Assessment Tool for Clinical Research, which is the main measure of decisional capacity in individuals with FXS [22]. Finally, we developed a sorting activity to identify the perceived reasons (both positive and negative) an individual may consent to participate in a clinical trial.

As the next step in our development process, we created audiovisual components to accompany the content of the tool. Universal design can be defined as a tool that is accessible and usable by everyone [23]. The approach stresses user awareness and emphasizes designs that can be used by as many people as possible while minimizing the need to adapt the product to support particular users, especially those with disabilities or limited function [23]. To develop the imagery and interaction model for the decision support tool, a graphic design artist created draft storyboards of initial content, audio, and a user interface that adhered to the principles of universal design. We

sought feedback on the storyboard from the project consultants, stakeholders, individuals with FXS, and their family members on the draft content. We undertook a collaborative and iterative process of refining and ultimately finalizing the content for the decision support tool.

Results

The results section focuses on initial testing of the decision support tool and how feedback received throughout each phase of testing further influenced the content and design of the tool. [Figure 2](#) outlines our project team's iterative testing and refinement approach that we used to enhance the decision support tool beyond what we had developed using the user-centered design process described in the Methods section.

Initial Concept Testing

We sought input from individuals with FXS on the 3 stylistic options for the decision support tool. We displayed a sample of each graphic style (simplistic, cartoon, and graphic novel, as [Figure 3](#) shows) and asked participants to vote on which style they most preferred. A total of 104 participants provided input on their preferred graphic style. Most, 45.2% (n=47), preferred the cartoon style, 36.5% (n=38) preferred the simplistic style, and the remaining 18.3% (n=19) preferred the graphic novel style.

Study staff also conducted in-depth, in-person interviews with 9 individuals with FXS to seek feedback on an early iteration of the tool's content. Interviews focused mainly on learning whether the images, text, and narration captured the clinical trial component as intended. Interviewers also asked the participants their opinions about the graphics used, suggestions for improvement, and whether the text and narration were understandable. Lower-functioning males with FXS expressed a preference for the cartoon graphic style; however, higher-functioning participants preferred the simplistic style, and we ultimately selected that design in order to appeal to these users.

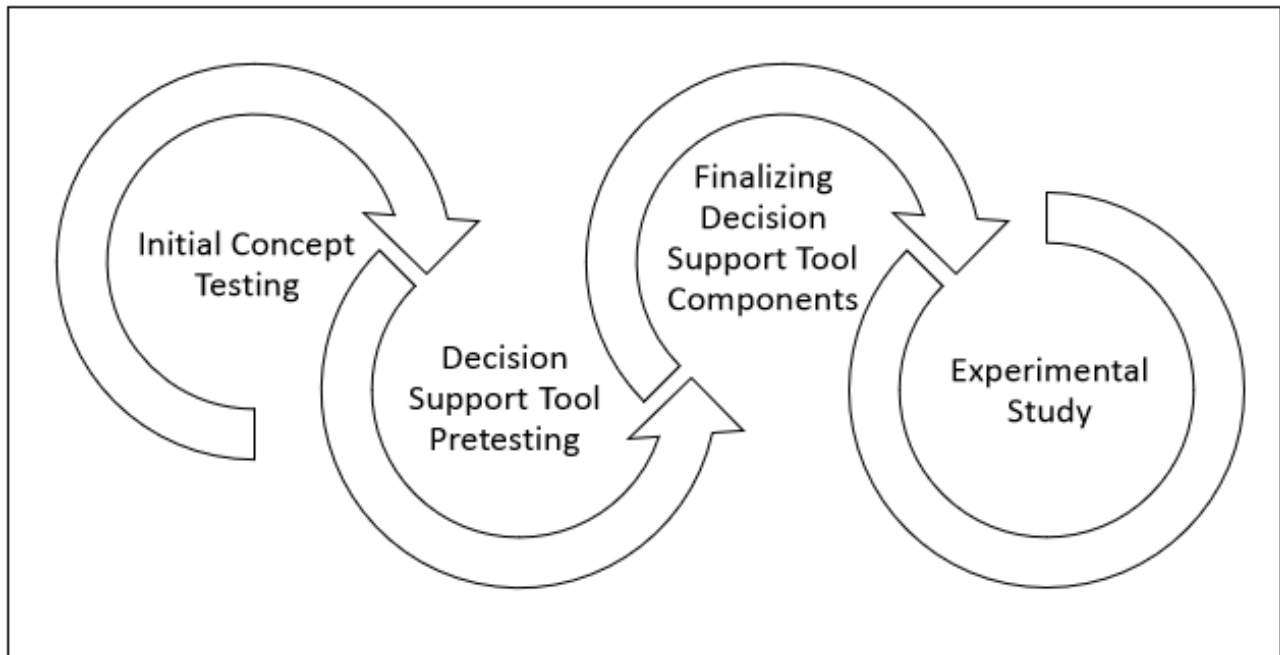
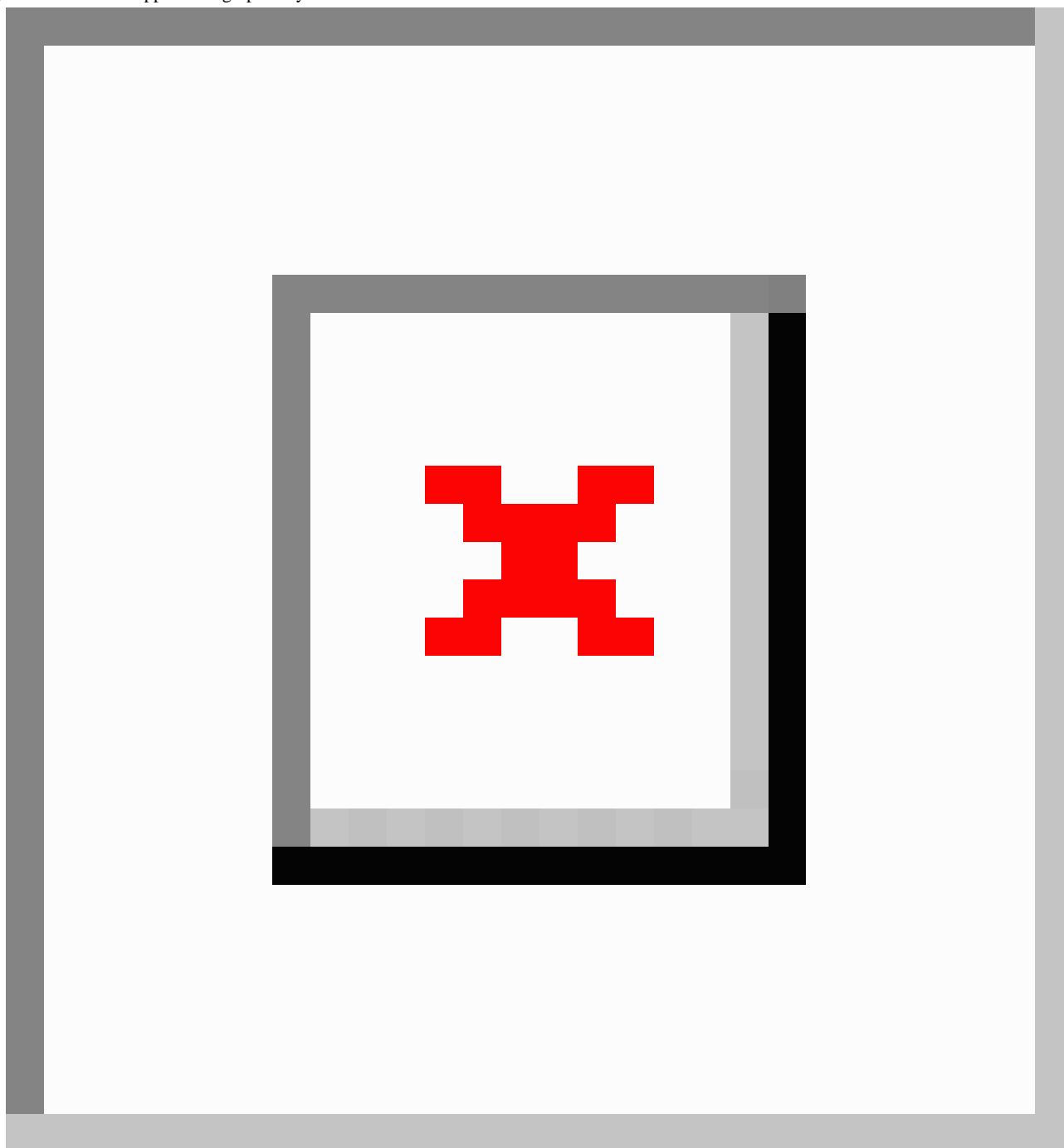
Figure 2. Decision support tool testing.

Figure 3. Decision support tool graphic styles.

Our interviews also revealed scenes that required modification and enhancements to increase comprehension among individuals with FXS. For one particular scene, we tested participants' comprehension of the clinical trial concept of placebo with an animation showing that some pills will contain medicine and others will not. Although participants liked the animation, they had difficulty grasping the concept. Participants also had difficulty understanding the concept of blinding, and that no one will know who will receive the trial drug. Similarly, participants were also confused by the concept of randomization, particularly regarding who decides which trial participant receives the drug versus the placebo. Participants had an easier time understanding more concrete concepts such as trial procedures (eg, providing a urine sample or having blood

drawn), and they were able to easily navigate through the different screens on the iPad and liked the narration and animations included throughout the tool.

Decision Support Tool Content

In the fall of 2015, we completed a draft of the tool composed of a series of 6 vignettes or interactive narratives, close-ended multiple-choice quiz questions, and a sorting activity. Each vignette discussed a separate component of the consent using plain language: study purpose, study involvement, how the study will work, study benefits, study risks, and withdrawing from the study. To evaluate each user's understanding of the content, multiple-choice questions followed each vignette. Before answering the multiple-choice questions, users were

given the option to watch the vignette again. If they answered the questions incorrectly, the vignette automatically replayed for the user 1 time and the multiple-choice question was presented again. A sorting activity was also used to facilitate a self-directed values clarification of the perceived reasons an individual may choose to participate or not participate in a clinical trial. Users were provided with 7 features of study participation (eg, “I would have to see my doctor several times” or “I might feel better”) and asked to sort each feature as a reason to be or not be in the study. Participants were required to sort a minimum of 2 features.

Pretesting and Finalizing the Decision Support Tool

We conducted incremental field testing on each component of the draft decision support tool: the vignettes, the quiz questions, and the sorting activity. On completion of the initial series of vignettes and in parallel with development of the quiz items, we pretested each component of the tool. We collected feedback from pretesting in a subsequent version while fielding the quiz component; we implemented input on the quiz during development of the sorting activity until we assembled the final decision support tool. The complete decision support tool underwent beta testing and internal software quality assurance testing to exercise the compiled decision support tool, verify skip logic, and confirm capture of accurate scoring metrics and session analytics. We completed the final version of the decision support tool in 2016.

Experimental Study

We initiated a two-arm randomized controlled trial (NCT02465931) in 2016 to compare the efficacy of the decision support tool with a standard verbal presentation of the consent material that mimicked typical consent practice. Participants were randomly assigned to receive the tablet-based decision support tool or the verbal script and paper consent. The trial protocol and outcomes will be published at a later date.

Discussion

Health Technologies to Support Complex Decision Making

The movement to empower patients through health technology to support complex decision making is gaining momentum. As the number of clinical trials targeting those with FXS increases, the goal of involving participants in the decision-making process will become increasingly important, emphasizing the need for tools that allow trial participants to become active members in the decision-making process. The process we describe strives to encourage those conducting trials with FXS patients to reevaluate how their participants are involved in the consenting process. The methods we employed in the design and development of the decision support tool described here can be developed, tested, and incorporated into routine practice. Further, although those with intellectual disability face challenges in making health decisions, those without such impairments are not immune to similar struggles.

Health literacy is defined as an individual’s ability to obtain, process, and understand health information and to use it to make health-related decisions [24]. Low health literacy has been

shown to be a systemic issue in the general population. The National Assessment of Adult Literacy [25] found that only 12% of US adults had proficient health literacy. This evidence illuminates deficits among most individuals who are seeking care from health care providers and are considering participation in clinical trials. Our decision support tool speaks to the potential benefits an interactive tool can provide for those making trial participation decisions, regardless of cognitive ability.

Digital Tools in the Informed Consent Process

The informed consent process is primed to leverage digital health resources given recent changes to the Common Rule in the United States that promote increasing understanding and engagement of research participants in the consent and research process. Interactive electronic informed consent material provides more adaptable content than traditional paper-based materials. The digital decision support tool can be deployed in a variety of settings, such as inpatient and outpatient clinics, hospitals, research facilities, or at home. The home setting enables a prospective trial participant to learn about the trial in a familiar and comfortable setting without perceiving potential undue pressure from medical or research personnel. The ability to go through the consent process at home also fosters shared decision making, as family members or those important to the individual can more easily review and openly discuss the information together. Additionally, the ability to use the tool at home provides convenience and reduces the need for travel to a clinic or physician’s office, which may be difficult for some individuals due to their living situation, financial status, or health issues, or the trial location.

Use of Agile Development for National Institutes of Health–Sponsored Studies

Agile software development is a group of methods in which requirements and solutions evolve through collaboration between self-organizing, cross-functional teams [26]. It promotes adaptive planning, evolutionary development, early delivery, and continuous improvement, enabling rapid and flexible response to change. Feature-driven development is an iterative and incremental software development process [27]. It is a lightweight, agile method for developing software that blends several industry-recognized best practices into a cohesive whole. These practices are driven from a client-valued functionality (feature) perspective to deliver tangible, working software repeatedly and in a timely manner.

Our development process for the decision support tool was consistent with an agile, feature-driven process. This can deliver value and yield a more efficient, responsive product, all while conforming to mandatory research processes such as evidence reviews, stakeholder engagement, regulatory compliance, and protection of human participants.

Involvement of an Interdisciplinary Team

The principle of “team science” addresses barriers associated with intervention development and implementation through engagement of an interdisciplinary team. This tactic brings together a variety of researchers with specialized expertise, approaches, and methodologies to solve complex problems [28,29]. The effectiveness of team science is evident in the

evolution of multiuniversity research teams, which often produce higher-impact research than do individual investigators [30]. Our project used a team science approach to sustain members' involvement and inform each phase of development for the decision support tool.

A team science approach is especially critical when considering digital health interventions, which require input and coordination from information technologists, researchers, and health care professionals [28,29]. In line with the team science approach, the development and implementation of the tablet-based decision support tool integrated input from diverse sources. Contributors consisted of clinicians, clinical implementation specialists, communication scientists, regulatory compliance experts, graphic designers, programmers, and field interview staff. We approached development of the tool as an integrated team and

remained integrated through completion of the randomized controlled trial.

Conclusion

Central to the success of this project were the team's recognition of the importance of a user-centered approach, stakeholder engagement and input, appreciation of interdisciplinarity, and willingness to explore and adapt commercial software methods and management techniques. The process and experiences described here may provide a model for other digital health design and development initiatives seeking to create more interactive and accessible decision support resources. Future research is needed on the impact of decision support tools in obtaining electronic informed consent and their influence on shared decision making and the user's decisional capacity.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Mobile app environmental scan results.

[[PDF File \(Adobe PDF File\), 31KB - resprot_v7i6e10525_app1.pdf](#)]

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Abbreviations

FXS: fragile X syndrome

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Original Paper

Development of a Tailored Intervention With Computerized Clinical Decision Support to Improve Quality of Care for Patients With Knee Osteoarthritis: Multi-Method Study

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Abstract

Background: Clinical practice patterns greatly diverge from evidence-based recommendations to manage knee osteoarthritis conservatively before resorting to surgery.

Objective: This study aimed to tailor a guideline-based computerized decision support (CDS) intervention that facilitates the conservative management of knee osteoarthritis.

Methods: Experts with backgrounds in clinical medicine, research, implementation, or health informatics suggested the most important recommendations for implementation, how to develop an implementation strategy, and how to form the CDS algorithms. In 6 focus group sessions, 8 general practitioners and 22 patients from Norway, Belgium, and Finland discussed the suggested CDS intervention and identified factors that would be most critical for the success of the intervention. The focus group moderators used the Guideline Implementation with DEcision Support checklist, which we developed to support consideration of CDS success factors.

Results: The experts prioritized 9 out of 22 recommendations for implementation. We formed the concept for 6 CDS algorithms to support implementation of these recommendations. The focus group suggested 59 unique factors that could affect the success of the presented CDS intervention. Five factors (out of the 59) were prioritized by focus group participants in every country, including the perceived potential to address the information needs of both patients and general practitioners; the credibility of CDS information; the timing of CDS for patients; and the need for personal dialogue about CDS between the general practitioner and the patient.

Conclusions: The focus group participants supported the CDS intervention as a tool to improve the quality of care for patients with knee osteoarthritis through shared, evidence-based decision making. We aim to develop and implement the CDS based on these study results. Future research should address optimal ways to (1) provide patient-directed CDS, (2) enable more patient-specific CDS within the context of patient complexity, and (3) maintain user engagement with CDS over time.

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KEYWORDS

decision support systems, clinical; practice guidelines as topic; guideline adherence; evidence-based medicine; osteoarthritis, knee; focus groups

Introduction

Background

Computerized decision support (CDS) is a technology that uses patient data to provide relevant medical knowledge when needed; it may improve adherence to evidence-based recommendations [1-3]. It can also target patients to facilitate shared decision making and to empower and motivate them [4-6]. Unfortunately, CDS is a complex intervention that has not consistently delivered positive returns on substantial investment [7-11]. Although multiple systematic reviews have provided some insights about these factors, we are only beginning to understand how to use CDS to improve care processes and patient outcomes [7,9,12-14].

We undertook the GUideline Implementation with DEcision Support (GUIDES) project to (1) investigate the factors that determine successful CDS implementation, (2) develop a checklist to address these factors, (3) develop a tailored CDS intervention to improve care, and (4) plan a multicountry cluster randomized controlled trial to assess the effectiveness of that intervention. This paper describes the methods and results for objective 3.

We chose CDS for knee osteoarthritis as a target medical condition for several reasons. The lifetime prevalence risk of symptomatic knee osteoarthritis is 45% [15] and is projected to increase with the rise of obesity and an aging population [3]. The guidelines for this condition largely agree on conservative management, including pharmacological and nonpharmacological interventions (eg, exercise, weight loss for overweight and obese patients) [16,17]. However, guideline adherence by health care professionals is remarkably low. A systematic review of studies assessing appropriateness of care found that only 36% of the eligible knee osteoarthritis patients receive the recommended nondrug treatment and 38% receive the recommended drug treatment in high-income countries [18]. This is opposed to a quality indicator score of nearly 80% for surgical referral. Although joint replacement surgery is effective, it is associated with significant perioperative complications, postoperative pain and functional limitation, and costs [19]. The number of joint replacements and the need for reoperations may be reduced if conservative modalities were exhausted first [20]. Knee arthroscopy is another frequently performed surgical procedure, despite guidelines with strong recommendations against its use [21].

Tailored implementation interventions are strategies that are designed to achieve desired changes in health care practice based on an assessment of determinants of health care practice [22]. Such strategies can include a single improvement intervention or they can be multifaceted. Determinants are factors that might prevent or enable adherence and these may relate to the health care professional, the patient, and the given context [23]. Tailored implementation can be used to improve care for different medical conditions and types of care practices.

A Cochrane systematic review provides evidence of the benefits of tailored implementation, but it remains unclear how best to tailor interventions [24]. In this paper, we describe our methods, processes, and experiences to contribute to learning for how to develop CDS interventions that require bridges between multiple research fields [25,26].

Objectives

The objective of this study was to determine how to tailor a CDS intervention for general practitioners (GPs) and patients that facilitates the conservative management of patients with knee osteoarthritis in Norway, Belgium, and Finland as defined by evidence-based recommendations [16,17].

Methods

Study Design

We collected input from 9 experts overall (with backgrounds in clinical medicine, research, implementation, or health informatics) and from 8 GPs and 22 patients coming from Norway, Belgium, and Finland. The choice of countries was pragmatic.

We tailored the intervention in 4 steps: (1) selection of the most important recommendations for implementation, (2) development of an implementation strategy, (3) forming the CDS intervention concept, and (4) identification of determinants that may affect the success of the suggested CDS strategy.

On the basis of the experience within the author group, we anticipated that a CDS intervention would be among the selected strategies in step 2 or that CDS at least would be able to facilitate other strategies.

We developed worksheets to provide support for steps 1 to 3 (see [Multimedia Appendix 1](#)). Eight experts of whom 4 were authors of this paper (SVDV, SF, GJ, and DS) used the worksheets to provide their considered judgment. We organized 6 focus groups, 2 in each country, to obtain input for step 4. The number of focus groups was a pragmatic choice. We discussed the results of each step within the project group and made decisions in consensus. We reported the focus group methods in accordance with agreed standards [27].

The project built on the results of the European Union (EU)-funded Tailored Implementation for Chronic Diseases project [22,23]. The author group included experts with a strong commitment to evidence-based medicine and broad expertise related to the clinical care of patients with knee osteoarthritis, and to the development, implementation, and evaluation of CDS [7,28-33].

Step 1: Selection of Recommendations

We identified evidence-based recommendations for the conservative management of knee osteoarthritis from existing overviews of guidelines [17,34]. Eight experts prioritized the most important recommendations for implementation by

assessing each recommendation for the following questions (worksheet A in [Multimedia Appendix 1](#)):

1. Is the recommendation feasible for practice?
2. Is adherence to the recommendation important?
3. Is there a large amount of inappropriate practice for this recommendation?

We only retained those recommendations where at least three-fourth of the experts agreed that it should be prioritized.

We also extracted information on the strength of recommendations, when this was presented according to the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach [35]. We agreed beforehand to consider both strong and conditional recommendations.

Step 2: Development of an Implementation Strategy

We identified published qualitative evidence syntheses to take account of the results of research on determinants of adherence to knee osteoarthritis recommendations [36-39]. For each determinant, 4 experts considered if it related to a specific recommendation or to all the recommendations, and they used worksheet B ([Multimedia Appendix 1](#)) to assess the following:

1. Is the determinant likely to have an important impact on adherence to the recommendation?
2. What would be a potential implementation strategy that takes into account this determinant?
3. Is the strategy likely to have an important impact on improving adherence?
4. Is the strategy feasible to implement?

The assessment of the determinants could lead to the selection of a single-faceted implementation strategy or to opting for a multifaceted package of implementation strategies.

Step 3: Forming the Computerized Decision Support Intervention Concept

We formed the concept of a CDS intervention to provide support in the electronic medical record (EMR). The CDS was intended to be operationalized with the Evidence-Based Medicine Electronic Decision Support System (EBMeDS; by Duodecim Medical Publications Ltd). EBMeDS receives structured patient data from EMRs and returns CDS based on programmed algorithms [30,40]. Computer scripts check relevant patient data in relation to predefined algorithms to determine if it would

be appropriate to present a given recommendation. EBMeDS can be linked to recommendations that are presented in the Making GRADE the Irresistible Choice (MAGIC) authoring and publication platform—an electronic platform for point-of-care evidence summaries and decision aids [6,28]. We chose to use EBMeDS and MAGICapp based on previous collaborations in research and implementation projects.

For each selected recommendation, we conceived a CDS algorithm. Five experts used worksheet C ([Multimedia Appendix 1](#)) to assess if it was appropriate to apply the suggested algorithms by using the following questions:

1. Is appropriate operationalization with CDS likely for this algorithm?
2. Is appropriate user response likely for this algorithm?

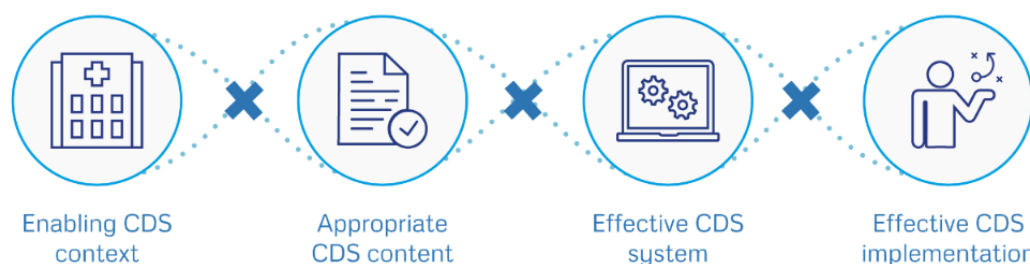
We did not use any majority thresholds for the selection of algorithms in this step.

Step 4: Focus Groups on Determinants of an Effective Computerized Decision Support Strategy for Knee Osteoarthritis

The focus groups covered the suggested CDS for the selected recommendations, the factors that determine successful use of CDS, and selection of the most important factors. During the focus group, we presented a hypothetical case of a patient with knee osteoarthritis, and we used screenshots to illustrate the suggested CDS strategy. We first identified determinants of successful CDS through brainstorming. When no additional factors were suggested by the participants, the moderator used the GUIDES checklist ([Figure 1](#)) to ask probing questions on factors that were not yet discussed [41,42]. A detailed interview guide is available in [Multimedia Appendix 2](#). We tested the interview guide on colleagues before the start of the actual focus groups.

We aimed to recruit 3 GPs and 3 knee osteoarthritis patients per focus group. We used convenience sampling based on our personal networks and recommendations from colleagues. We included patients from different age groups, with different degrees of osteoarthritis and patients having osteoarthritis as a single condition together with patients having comorbidities. We ensured that patients and GPs in the same group did not have a personal doctor-patient relation. We also ensured that there were at least as many patients as GPs to increase patients' confidence when expressing views and experiences.

Figure 1. The GUIDeline Implementation with DEcision Support (GUIDES) checklist contains 16 factors covered by 4 domains that potentially impact on the success of computerized decision support (CDS) to implement recommendations. The CDS context domain focuses on the circumstances in which CDS can be potentially successful; the CDS content domain focuses on the factors shaping the success of the advice produced by the CDS system; the CDS system domain focuses on the features belonging to the CDS tool; and the CDS implementation domain refers to the factors affecting the CDS integration in practice settings.



We contacted every participant before the focus group to collect informed consent and to address any questions. The focus groups took place in meeting rooms of the participating institutions.

SVDV (male) moderated the focus groups in Norway and Belgium and TK (female) in Finland. TK was experienced in conducting focus groups, and SVDV received training beforehand [30,32]. The moderators emphasized that both positive and negative feedback about the CDS intervention was important. We audio-recorded each focus group and an observer took notes. We transcribed key parts of the focus groups, but we did not do a full transcription of the recordings.

Data Analysis

We transcribed the data from the focus groups anonymously and applied the framework analysis approach [43]. One researcher (SVDV) analyzed the transcribed parts of the interview recordings and used an Excel worksheet to extract all quotes, including determinants and alternative or additional strategies for the suggested CDS intervention that the participants mentioned in step 4. We classified the data according to the GUIDES checklist (Multimedia Appendix 3). If we could not link quotes to a specific field in the chosen checklist, we categorized this as general. SVDV evaluated which quotes were related to others in order to group them. We then labeled and analyzed the quotes as such. For every labeled item, we explored if it was linked to the focus group procedure (without GUIDES checklist through brainstorming vs through a structured discussion based on the GUIDES checklist). One researcher (SF) double-checked the grouping, labeling, and analysis. Three researchers who participated in the focus groups (SF, TK, and DS) double-checked the reporting of the interviews. The researchers resolved disagreement by consensus.

Ethics Approval and Consent

The Regional Committee for Medical Research Ethics in South East Norway and the University Hospitals Leuven Medical Ethics Committee in Belgium waived the requirement to seek ethical approval. In Finland, approval for the study was received from the Ethics Committee of the Pirkanmaa Hospital District.

Availability of Data and Material

All data generated or analyzed during this study are included in this published paper and its Multimedia Appendix files.

Results

Selection of Recommendations, Implementation Strategy, and Potential Computerized Decision Support Intervention

We selected 9 recommendations (Textbox 1) out of 22 recommendations that we extracted from the overviews of knee osteoarthritis guidelines. Multimedia Appendix 4 provides details on the ratings for every recommendation. The Finnish experts did not prioritize the recommendation on clinical diagnosis, as x-ray is a usual part of the diagnostic assessment if long-term treatment is required.

Two guidelines graded their recommendations according to GRADE, and we extracted information on the strength of the recommendations based on these guidelines [21,44]. Five prioritized recommendations were strong recommendations, 3 were conditional recommendations, and no strength was currently available for the diagnostic recommendation.

We extracted 30 factors that might affect adherence to knee osteoarthritis recommendations from 4 qualitative evidence syntheses [36-39]. They were categorized in 4 domains: guideline factors, health professional factors, patient factors, and incentives and resource factors [23]. Guideline factors addressed clarity, specificity, and ease of implementation of recommendations. Key themes for health professional factors were personal opinions and attitudes about the importance of knee osteoarthritis and its progression and management. Another factor is the information needs of health care professionals about recommended practice. Patient factors related to information needs; shared decision making; and the role of patient opinion, motivation, and behavior.

Both health professional and patient factors contributed to obtaining a timely diagnosis. Incentives and resources factors included financial incentives and disincentives to adherence and the limited time available during a patient consultation. The experts assessed these determinants and confirmed that a guideline-based CDS strategy was appropriate, combined with a need for health care provider education, the availability of patient information, and strategies to support patients in realizing lifestyle changes. We did not consider actions to make health system changes because we could not take direct responsibility for this and judged that such changes were not feasible in the context of our project.

Textbox 1. Overview of the prioritized recommendations for knee osteoarthritis.

- A clinical assessment is sufficient to diagnose knee osteoarthritis [45]: no grade of recommendation available (NA)
- Patients with knee osteoarthritis should receive self-management information and education [17]: conditional recommendation (CR)
- Patients who are overweight should be encouraged to lose weight [17]: strong recommendation (SR)
- Low-impact aerobic exercise (land or water based) should be recommended to patients [17]: SR
- Cardiovascular or strengthening exercises should be recommended to patients [17]: SR
- Oral nonsteroidal anti-inflammatory drug (NSAID) should only be used after acetaminophen [17]: CR
- Gastroprotection for high-risk patients [17]: SR
- Topical NSAID should be used as adjunctive and alternative to oral agents [17]: CR
- Arthroscopy with debridement is not recommended for the management of symptomatic knee osteoarthritis [17]: SR

We formed the concept for 6 algorithm-based CDS scripts to support implementation of the prioritized recommendations:

1. A first script suggests to the GP to consider if the diagnosis of knee osteoarthritis is relevant in patients aged above 45 years with a knee complaint code registered in the EMR, and it presents the diagnostic criteria.
2. Another script suggests discussing the treatment plan for patients with a knee osteoarthritis diagnosis and to provide patient information. This reminder links to patient information and patient decision aids that provide detailed information on the benefits and harms of every treatment option and the related practical issues.
3. For every knee osteoarthritis patient, a reminder shows that exercise is recommended.
4. In patients that are overweight or obese, a reminder suggests dietary counseling and bariatric surgery if the body mass index (BMI) is above 35 kg/m².
5. If the BMI value for a patient with knee osteoarthritis is missing or when its calculation is older than 2 years, a reminder suggests adding the missing clinical data in the EMR.
6. The last script generates a reminder in patients with a prescription for oral NSAIDs to consider topical NSAIDs and/or paracetamol.

Figures 2 and 3 provide an illustration for parts of the CDS and the consultation decision aids. Multimedia Appendix 2 provides further illustrations.

Determinants Affecting Success of the Suggested Computerized Decision Support Strategy for Knee Osteoarthritis

We conducted 6 focus groups (2 in each country). A total of 22 patients and 8 GPs participated in the focus groups. In Finland, all the participants were patients. No participants dropped out. Moreover, 19 patient participants were females, and only 3 were

males. Their age ranged from 26 to 85 years. GP participants were mainly male, and only 1 was female. Age ranged from 29 to 69 years.

The participants suggested 211 factors that might affect the success of the presented CDS intervention. When we combined the factors that are related or somewhat related, we ended up with 59 unique factors. Of the unique factors, 14% (8/59) were identified by patients only, 39% (23/59) by GPs only, and 47% (28/59) by GPs in 1 group and by patients in another group. The median number of unique factors suggested per focus group was 31 (range 15-37).

The participants selected 47 factors that they considered most important. Nine factors were discussed in each country, among which 5 factors were also prioritized in each country (see Textbox 2). We grouped the factors in 7 categories that we describe in detail below. Multimedia Appendix 5 lists all the suggested factors and indicates if the factors were prioritized and if they were related to one or more countries.

Factors Related to Information Needs for Patients

Participants thought that patient-directed CDS could be a good strategy by providing reliable information directly to patients. Some found that it is particularly useful, given the time limitations of a consultation, and that it could reduce unwarranted delays when ordering consultations. Both patients and GPs mentioned that informing patients better can increase the potential for shared decision making:

Patients need direct access to CDS so that they can prepare themselves for a consultation. [Patient, Norway]

It is an advantage when reliable information can be sent to the patient, because GPs often have to use time to reassure patients that have read inappropriate information from unreliable sources. [GP, Belgium]

Figure 2. Illustration of the generated computerized decision support (CDS) in the style of Evidence-Based Medicine Electronic Decision Support System (EBMeDS) after having entered the body mass index (BMI) and after having prescribed an oral nonsteroidal anti-inflammatory drug (NSAID). On the basis of the patient data in the electronic record, the CDS system presents patient-specific reminders, links to guidelines, and practical tools. When clicking on the reminder, the general practitioner (GP) receives more information about the recommendation, how this reminder works, and on which guideline(s) the information is based. ICPC: International Classification of Primary Care, second edition.

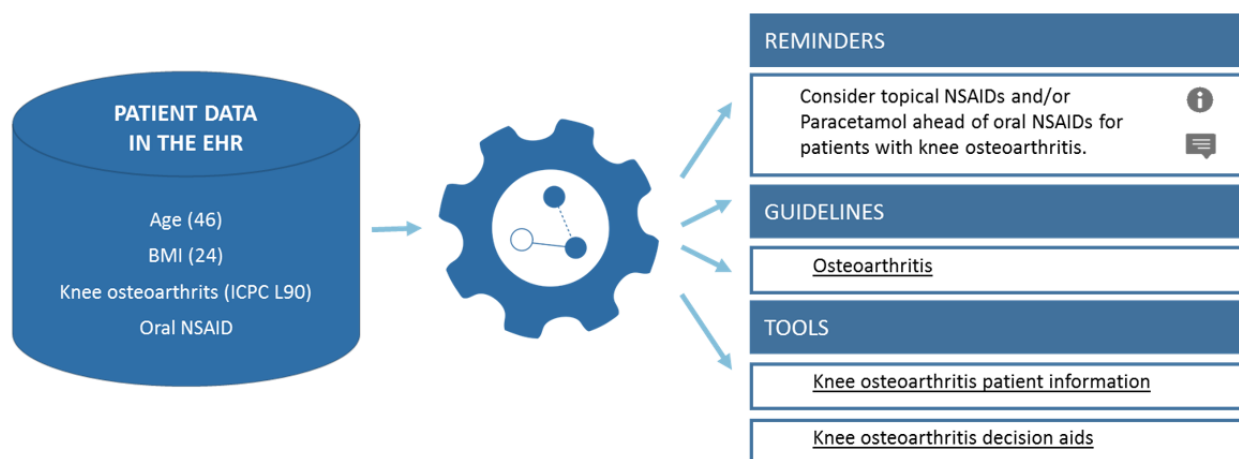
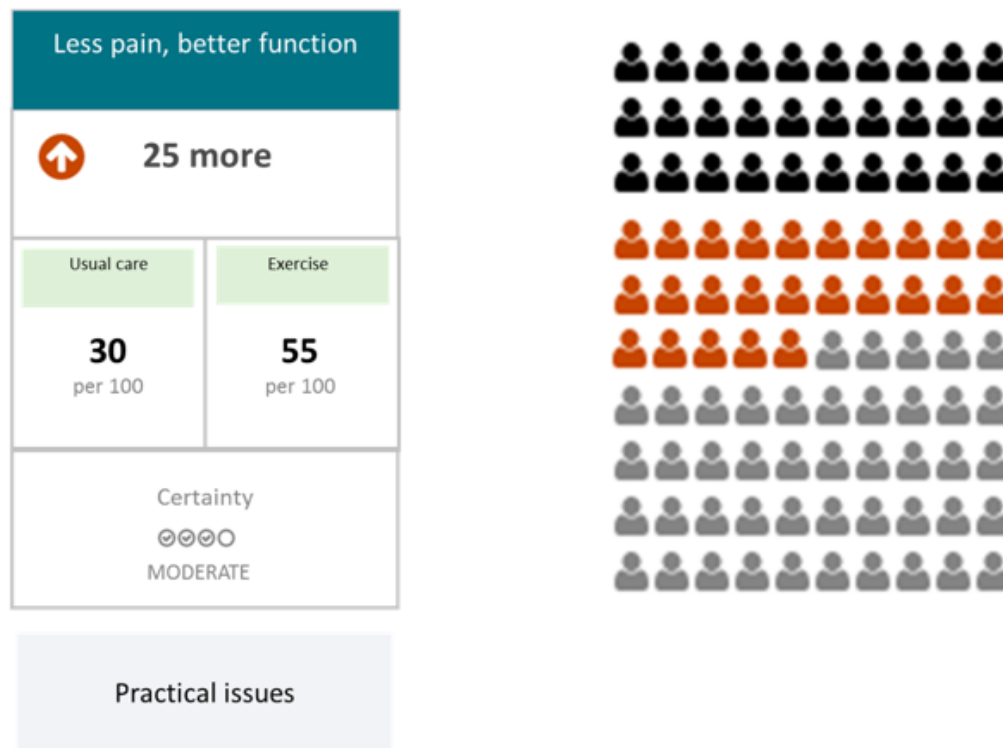


Figure 3. Illustration of the decision aid on exercise in the style of MAGICapp. The general practitioners (GPs) and the patient can use this to discuss the benefits and practical issues for potential treatment options. The decision aid provides graphic displays of the benefits and harms of different treatment options together with information about certainty in estimates of effect according to Grades of Recommendation Assessment, Development, and Evaluation (GRADE). When clicking on the “Practical issues” button, another information layer opens with additional information (eg, description of the procedure, adverse effects).

Among 100 patients like you, on average with exercise



Several participants preferred that the GP would act as an intermediate recipient of the patient-directed CDS:

An alternative approach is that the GP gets an overview of the CDS for the patient and then decides if it is relevant to forward it to the patient. [GP, Norway]

Other patients might prefer not to receive any CDS information at all. This might be influenced by previous experiences with information technology. GPs do not always know if a patient wants additional information, and posters or flyers in the waiting room could inform patients that they can ask their GP for patient information.

Participants mentioned some potentially negative consequences of providing CDS directly to patients, including anxiety, inappropriate management, and the risk that CDS might replace the personal contact with the GP. Multiple GPs and patients preferred to deliver CDS for patients during the consultation so that the GP can advise the patient in person:

GPs should assess the CDS and give treatment advice that is suitable for that patient. [Patient, Finland]

Patients recognized the importance of knowledge about what to do, but mentioned other barriers. Personal beliefs and desires

about tests or treatments can be strong. Patients may need support to help achieve lifestyle changes, and some gave the example of physiotherapy for patients that are less motivated. Another patient expressed the need for more practical information:

More information for patient is needed about how to live with osteoarthritis. CDS could inform about osteoarthritis schools for patients and patient support groups. [Patient, Norway]

Factors Related to Information Needs for General Practitioners

CDS could help GPs not to forget certain treatment options and to stay updated about new or changed recommendations. A patient suggested that the CDS intervention could make GPs more attentive to osteoarthritis. One GP mentioned that CDS should not limit the treatment choices of GPs. Furthermore, CDS should inform and alert in a constructive way but not criticize the GP:

It is obvious that all GPs do not know all treatment options to all diseases, so CDS could help them. [Patient, Finland]

Textbox 2. Nine factors (grouped into themes) that may affect success for the suggested computerized decision support (CDS) strategy for knee osteoarthritis and that general practitioners (GPs) and patients suggested in Norway, Finland, and Belgium. Five factors were prioritized in each of the 3 countries.

<p><i>Patient needs</i></p> <ul style="list-style-type: none"> • Potential to address the information needs and demands for patients (<i>prioritized</i>) • Acceptability of CDS for patients • Need for personal dialogue about the CDS between the GP and patient (<i>prioritized</i>) <p><i>GP needs</i></p> <ul style="list-style-type: none"> • Potential to address the information needs for GPs (<i>prioritized</i>) <p><i>Patient data</i></p> <ul style="list-style-type: none"> • Accuracy and completeness of the available patient data in the electronic medical record (EMR) • Benefits of CDS on quality of patient data in the EMR <p><i>Workflow and workload</i></p> <ul style="list-style-type: none"> • No common factors for the 3 countries <p><i>CDS content</i></p> <ul style="list-style-type: none"> • Credibility of the CDS information (<i>prioritized</i>) <p><i>CDS system</i></p> <ul style="list-style-type: none"> • Effort required to use the CDS system • Timing of delivery of CDS for patients (<i>prioritized</i>) <p><i>CDS implementation</i></p> <ul style="list-style-type: none"> • No common factors for the 3 countries
--

GPs asked if CDS could help them to identify patients that are coping badly with their disease. This would make it possible to devote extra attention to those patients that need it most.

A patient commented on the limitations of CDS:

Technology alone is not enough, a lot has to do with the personal contact between the patient and the physician, and the physician needs to know the patient's perspective. [Patient, Norway]

Several patients suggested that other health care professionals should also receive CDS.

Factors Related to Patient Data

GPs mentioned that the patient's EMR could have data gaps. Often, GPs record symptoms instead of a diagnosis. Some GPs found it positive that CDS could identify and help filling gaps in the patient's record. Some said that CDS would motivate them to improve the quality of their EMR. Another GP mentioned that requests to register extra data (such as BMI) should be limited:

Physicians should only be asked to enter patient data when this is having a positive impact on the patient outcome. [GP, Norway]

Now I have to bring my medical data on a paper to the GP or occupational therapist. [Patient, Finland]

Both patients and professionals discussed that additional patient data are needed to allow good CDS. Data on patient adherence and effect of the treatment were mentioned several times. GPs also suggested registering the diagnosis or complaint for the encounter. Knowledge about the reason for encounter could help GPs to prepare for the consultation and could prevent the CDS from generating information that is irrelevant for the reason for the encounter:

It would be interesting if the GP could indicate the reason for the encounter and that CDS is triggered accordingly. [GP, Norway]

Factors Related to Workflow and Workload

The limited time to use and discuss the CDS during a patient encounter is a barrier, especially when patients want to discuss multiple problems. Therefore, CDS needs to be well integrated. Given the time pressure, CDS can create stress for GPs. It may be necessary to plan an additional consultation to discuss the information given by the CDS.

CDS could also save time for GPs if it facilitates fast information retrieval. Some GPs mentioned that it is faster to use CDS than to find information in a book:

CDS should fit in the workflow so that it has no negative impact on the amount of patients seen by the clinician. [GP, Belgium]

A challenge for timely CDS is that the GPs often do not enter the diagnosis for new complaints directly in the EMR. A risk with CDS is that it might disturb the personal contact between the patient and the GP.

Factors Related to the Computerized Decision Support Content

CDS should recommend specific action. Many participants requested more information about which type of exercise works best:

I got the instruction to bike 30 minutes/day. It has never been clear why I had to do exactly this training. Is this type of training more beneficial than others?
[Patient, Norway]

A GP mentioned that CDS should provide nuances that are specific to a patient and that this can be too big of a challenge for some problems. It might only be possible to provide CDS if the condition and the recommended action can be defined in sufficient detail.

Some GPs emphasized that CDS has to be based on evidence-based guidelines that are up to date. The participants perceived the presented CDS intervention as a reliable tool. The certainty of the evidence should be clear for every CDS recommendation. Some GPs found detailed information about the treatment effect important, whereas other GPs considered this information as trivial facts. Several participants considered it a limitation that the CDS presents mean treatment effects, when the effect that an individual patient experiences can be different from these mean effects.

GPs commented that CDS should be relevant for the patient's problem and that irrelevant CDS content can be disturbing:

CDS can diverge the focus of the consultation to the topics suggested by the CDS instead of the problem raised by the patient. [GP, Norway]

Insight in how the CDS is triggered is desirable in case GPs have doubts about the CDS.

Those that implement CDS should carefully reflect over the amount of CDS, because too much information can overload both patients and GPs:

When the information becomes too much, then you lose focus. [GP, Norway]

The CDS should not overload the patient, too much information will lead to forgetting parts of it. [GP, Belgium]

Both patients and GPs suggested to divide CDS over time, for example, over different consultations for the same patient. In the case of patients with comorbidities, the CDS system should prioritize which content is most important. A GP commented that CDS should cover a minimum number of potential patient problems:

CDS should at least cover 100 to 200 diagnoses before it becomes interesting to use. [GP, Norway]

Factors Related to the Computerized Decision Support System

CDS should be easy to use. The system should work fast and with minimal data traffic. One GP noticed that experience with the system might reduce the time required to use it:

Within the EMR, physicians already need to click a lot. CDS requires additional clicks and I don't know if I am motivated to make that additional effort. [GP, Belgium]

GPs desired CDS that is short and immediately understandable. Some GPs suggested a multilayered approach where it is possible to click for further information. Several GPs emphasized the important role of a visual display that includes illustrations.

Patients suggested multiple channels to deliver patient-directed CDS:

CDS should appear in all the communication channels that a patient uses. For example a smartphone, e-mailbox, etc. [Patient, Finland]

Patients do not have access to CDS that is presented in the EMR. Can the electronic patient record be an instrument to provide CDS to patients? [Patient, Norway]

GPs mentioned that they should have control over the system, including the potential to customize which CDS they will receive and the option to receive CDS only on demand. Other GPs preferred CDS that is provided automatically but not as pop-ups. GPs expressed different preferences regarding the timing of the CDS. Some found CDS most effective during the consultation, whereas others would read CDS before the patient encounter if they knew the contact reason.

A challenge is that the GPs over time might be less interested in the CDS information:

After a while you will no longer give attention to the information that you have read several times before. This includes the risk that you do not notice that new information is available. [GP, Belgium]

Factors Related to the Computerized Decision Support Implementation

Participants mentioned that the CDS must be intuitive, but the GPs and patients should always receive information about the system beforehand. Some GPs also requested training, even for intuitive systems. Those responsible for implementing the CDS system should market the CDS with clear examples of the advantage of CDS. One GP suggested marketing CDS toward patients, so that patients would ask if their GP is using such a system:

The system should be marketed and the best strategy is to demonstrate success through the involvement of superusers or through demonstration in pilots. [GP, Norway]

Participants discussed the need to monitor system performance and referred to other eHealth initiatives with adequate electronic feedback channels. Sufficient technical support and budget is

needed. Participants suggested public governance of CDS. Some thought it could also be private but not financed by the drug industry:

The system should not be incomplete when it is implemented, because then it will not be a practical solution to the user; The system should be continuously improved. [Patients, Finland]

Discussion

Principal Findings

The results of this study inform the development and implementation of a tailored CDS intervention. The experts prioritized 9 knee osteoarthritis recommendations for implementation. To implement these recommendations, we selected CDS combined with education for GPs, and patient information and support to achieve lifestyle changes. We formed the concept for this CDS intervention and discussed it with patients and GPs during focus groups. Both patients and GPs found that the strategy has potential to improve the quality of health care for patients with knee osteoarthritis. Use of the GUIDES checklist allowed us to identify additional factors that would otherwise have been missed by the focus group. These findings have been submitted for publication to *Implementation Science* (S Van de Velde, unpublished data, May 2018).

Strengths and Limitations

We followed a systematic approach, including considered judgment by experts and focus groups with patients and GPs, to build knowledge that can inform the development of a tailored CDS intervention to improve the quality of care for patients with knee osteoarthritis [23,46].

Although it seems intuitive to tailor interventions to the determinants of practice, existing evidence indicates that we can only expect moderate effects on outcomes through tailored implementation [24,47]. Our systematic approach was also a lengthy and resource-intensive process. When embarking on a complex intervention, we consider it good practice to do this systematically, in line with guidance from the UK Medical Research Council on complex interventions [48]. This helps to ensure a greater return on investment and prevents unnecessary trial and error or unintended negative consequences.

We involved a broad range of stakeholders during the development of the intervention. We assume that this multiperspective approach allowed us to identify the diversity of factors. Some of the health care professionals and researchers had a professional relationship with the authors, but as our only interest was to improve the quality of care, we do not expect that this had an influence on the feedback.

Only 8 GPs participated in the focus groups compared with 22 patients. It was difficult in each of the participating countries to find GP participants for the focus groups. In Finland, only patients participated in the focus groups, as we were unable to recruit GPs there. Our comparison of the factors identified per country is by consequence incomplete.

Our multicountry approach increases the generalizability of the strategy. Most of the factors seem to apply to the 3 countries, and it is plausible that the CDS intervention can also be implemented in other countries. However, we did not systematically evaluate generalizability to other countries that may share less similarities than Norway, Belgium, and Finland.

Implications

Any decision to use CDS, other interventions, or additional implementation strategies should be based on an assessment of the determinants of health care practice that affect whether the desired changes can be achieved [23]. Furthermore, it is important to be aware of the factors shaping CDS effectiveness [9]. This study has advanced the understanding of such determinants and CDS success factors.

We now aim to develop the CDS based on the input from the focus group discussions. We then plan to conduct a usability evaluation among the users and an evaluation of the accuracy of the CDS recommendations and the relevant patient data in the EMR [49-51]. We intend to evaluate this intervention in a multicountry cluster randomized controlled trial and assess its cost-effectiveness.

The evidence on the effect of CDS on patient outcomes is very uncertain, and only 1 trial has been conducted so far on patients with knee osteoarthritis. That trial studied the effect of CDS for GPs combined with a patient-directed intervention and found slightly better function and increased physical activity at 12 months but no differences for pain, depressive symptoms, and BMI [52].

Multiple key questions emerged from the focus groups. First, we do not know the best way to provide patient-directed CDS. Approaches previously used should be investigated within this context [53,54]. In addition, the field of CDS needs to engage on a discussion with the field of patient decision aids [55]. Second, it is not clear how best to collect and use additional patient data to enable more patient-specific CDS. Integrating evidence from reliable analyses of patient subgroups in randomized trials and systematic reviews may provide a reasonable starting point to making CDS more patient-specific [56,57]. Third, it is not clear how to maintain users' interest and engagement with the CDS over time. CDS research needs to explore how sustainability can be achieved [58-60]. A systematic review of factors that improve long-term use of CDS may provide a starting point for this agenda.

Conclusions

The focus group participants expressed their support for the CDS intervention as a tool to improve the quality of care and the outcomes for patients with knee osteoarthritis through shared, evidence-based decision making. GPs and patients perceived the strategy as helpful for their information needs. It might also improve the quality of patient data in the EMR. It is important that GPs can use the CDS with limited effort, and the usability of the CDS should be tested before full-scale implementation.

Acknowledgments

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Authors' Contributions

SVDV wrote this paper with all authors commenting on drafts and approving the final version. SF is the guarantor for this study. SVDV and TK moderated the focus groups, and SF and DS participated as observers to the focus groups. SDVD, SF, DS, TK, IK, and GJ completed one or more worksheets for the concept of the CDS intervention.

Conflicts of Interest

IK is the founder and leader of the EBMeDS system for CDS. PV is director of the MAGIC nonprofit initiative and research and innovation program MAGICorg. SVDV has started doing research for MAGIC after completion of this study. The other authors of this paper declare that they have no financial or intellectual conflicts of interest.

Multimedia Appendix 1

Worksheets.

[[PDF File \(Adobe PDF File\), 51KB - resprot_v7i6e154_app1.pdf](#)]

Multimedia Appendix 2

Interview guide.

[[PDF File \(Adobe PDF File\), 575KB - resprot_v7i6e154_app2.pdf](#)]

Multimedia Appendix 3

GUideline Implementation with DEcision Support (GUIDES) checklist.

[[PDF File \(Adobe PDF File\), 44KB - resprot_v7i6e154_app3.pdf](#)]

Multimedia Appendix 4

Prioritization of recommendations.

[[PDF File \(Adobe PDF File\), 40KB - resprot_v7i6e154_app4.pdf](#)]

Multimedia Appendix 5

Focus group data.

[[PDF File \(Adobe PDF File\), 396KB - resprot_v7i6e154_app5.pdf](#)]

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Abbreviations

BMI: body mass index

CDS: computerized decision support

EBMeDS: Evidence-Based Medicine Electronic Decision Support System

EMR: electronic medical record

EU: European Union

GP: general practitioner

GRADE: Grades of Recommendation Assessment, Development, and Evaluation

GUIDES: GUIDeline Implementation with DEcision Support

MAGIC: Making GRADE the Irresistible Choice

NSAID: nonsteroidal anti-inflammatory drug

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Protocol

Integrated Hepatitis C Care for People Who Inject Drugs (Heplink): Protocol for a Feasibility Study in Primary Care

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Abstract

Background: Hepatitis C virus (HCV) infection is a major cause of chronic liver disease and death. Drug use remains the significant cause of new infections in the European Union, with estimates of HCV antibody prevalence among people who inject drugs ranging from 5% to 90% in 29 European countries. In Ireland and the European Union, primary care is a key area to focus efforts to enhance HCV diagnosis and treatment among people who inject drugs.

Objective: The Heplink study aims to improve HCV care outcomes among opiate substitution therapy (OST) patients in general practice by developing an integrated model of HCV care and evaluating its feasibility, acceptability, and likely efficacy.

Methods: The integrated model of care comprises education of community practitioners, outreach of an HCV-trained nurse into general practitioner (GP) practices, and enhanced access of patients to community-based evaluation of their HCV disease (including a novel approach to diagnosis, that is, Echosens FibroScan Mini 430). A total of 24 OST-prescribing GP practices were recruited from the professional networks and databases of members of the research consortium. Patients were eligible if they are aged ≥ 18 years, on OST, and attend the practice for any reason during the recruitment period. Baseline data on HCV care processes and outcomes were extracted from the clinical records of participating patients.

Results: This study is ongoing and has the potential to make an important impact on patient care and provide high-quality evidence to help GPs make important decisions on HCV testing and onward referral.

Conclusions: A substantial proportion of HCV-positive patients on OST in general practice are not engaged with specialist hospital services but qualify for direct-acting antiviral drugs treatment. The Heplink model has the potential to reduce HCV-related morbidity and mortality.

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KEYWORDS

hepatitis C; primary health care; general practice; opiate substitution treatment

Introduction

Hepatitis C as a Global Challenge

With approximately 71 million people affected worldwide and 399,000 related deaths, chronic hepatitis C virus (HCV) infection is associated with considerable morbidity, including cirrhosis and hepatocellular carcinoma [1]. Injecting drug use remains the significant cause of new infections in the European Union, with estimates of HCV antibody prevalence among people who inject drugs (PWID) ranging from 5% to 90% in 29 European countries [2]. With successful treatment and viral eradication, recent data have demonstrated decreases in all-cause mortality, mortality due to cirrhosis, and the incidence of hepatocellular carcinoma [3-5].

Recently developed HCV direct-acting antiviral drugs are well tolerated and delivered for shorter courses (8-12 weeks), with trials reporting more than 90% cure rates among PWID [6]. Despite these highly effective and simplified therapeutic regimens, many people at risk are unaware of their infection, and obstacles limit access to HCV care, resulting in many patients not being treated [7].

Notwithstanding these challenges, the World Health Organization has set a goal of eliminating viral hepatitis as a major public health threat by 2030, reducing new chronic infections by 90% and reducing mortality by 65% [8]. In most countries, the scale-up of HCV treatment for PWID, along with needle and syringe programs and opiate substitution therapy (OST), will be key to these targets being achieved.

Enhancing Access to Treatment

Reaching and engaging PWID with HCV are key challenges, given the prohibition surrounding illicit and injecting drug use and the resultant stigma and discrimination concerns and possible mistrust of health services [9]. Community and peer involvement is likely to be critical to the success of HCV prevention programs for PWID. It has also been hypothesized by some clinicians and researchers that successful treatment of HCV in PWID can improve recovery and engagement with addiction treatment [10].

Blood tests and liver biopsy were historically the standard approach to assess the need for treatment in those with chronic HCV infection. However, many patients have defaulted from HCV care because of perceived dangers associated with liver biopsy [11]. More recently, alternative diagnostic modalities including liver stiffness measurement by transient elastography (Echosens FibroScan Mini 430) have resulted in noninvasive approaches to stage fibrosis. Several European studies have recently reported on the feasibility of fibroscanning as a screening tool for drug users, with high rates of acceptance and uptake within various treatment and street outreach settings [12,13]. The mobility of this equipment means it can be transported to community sites to access patients, and for PWID, this procedure can help assess disease severity, enhance HCV assessment, reduce patient identified barriers, target therapy, and enable the triage of patients for more immediate care [14-16].

The Role of Primary and Community-Based Care

In Ireland and the European Union, primary care is increasingly providing long-term care for PWID. Although screening and identification practices are inconsistent, 62% to 81% of this population are infected with HCV [17,18]. Furthermore, research indicates 35% of patients attending general practitioners (GPs) for OST in Ireland also had problem alcohol use (PAU) [19], and a subsequent qualitative study highlighted the need for primary care to address this problem through screening and brief intervention [20]. The study recommended initial screening for PAU by the patient's GP using the Alcohol Use Disorders Identification Test (AUDIT) screening tool [21] and providing feedback on results in all cases with positive findings through a brief intervention involving advice on minimizing alcohol harm, encouraging a reduction in alcohol consumption, and initiating referral to specialists when needed. Thus, primary care is a key area to focus efforts to enhance HCV diagnosis and treatment among PWID. However, a number of challenges exist in this regard, including for PWID: lack of awareness, fear of side effects for HCV drugs, possible poor adherence, and comorbid conditions; and for health care providers, limited knowledge and communication difficulties may be problematic [16,22,23]. These challenges can be addressed through education, audit and feedback, and liaison nurse support [24,25]. Research has demonstrated that if adequately supported, primary care and specifically general practice could adequately screen for HCV [26]. Research indicates that offering primary care practice staff training on the epidemiology, diagnosis, and management of HCV infection, so increasing testing of HCV was cost-effective [27]. Furthermore, testing PWID in primary care may also identify patients who have been diagnosed previously but have not been referred to, or failed to attend specialist care, offering the opportunity to review and follow-up such referrals.

Aims

This Heplink study forms part of a European Union-funded program of research (HepCare Europe) which aims to optimize hepatitis C diagnosis; linkage between primary, secondary, and outreach community care; and access to treatment for at risk-populations in the European Union.

The Heplink study focuses specifically on developing complex interventions to enhance community-based HCV treatment and improve the HCV care pathway between primary care and secondary care. As such, Heplink is a prospective, nonrandomized pre-post intervention feasibility study in primary care to identify and invite patients on OST to undergo testing, with referral to secondary care, where appropriate. We will evaluate the feasibility, acceptability, and likely efficacy of this approach quantitatively, qualitatively, and through assessing its cost-effectiveness. The specific objectives of the study are to develop and implement an integrated model of HCV care and evaluate its feasibility, acceptability, likely efficacy, and cost-effectiveness in practice.

Methods

Study Design and Setting

This is a prospective, nonrandomized, pre-post intervention feasibility study to be conducted in OST-prescribing general practices from three sites across the Hepcare Europe consortium (Dublin, London, and Seville). Practices will be given written information on the study and asked to indicate their interest in participating. Our recent experience recruiting general practices [28,29] has taught us the importance of a researcher promptly following up an expression of interest from a GP to fully explain the study and highlight what will be required from the GP in terms of time and commitment to the study. As such, practices who express an interest in participating will be contacted by a member of the research team to explain the aims of the study and what is required.

Study Population

A sample of 24 OST-prescribing GP practices will be recruited from the professional networks of members of the research consortium.

Practices will be eligible to participate if they are registered to prescribe methadone and have at least 10 patients currently receiving OST; agree to participate in practice audit; and (3) agree to facilitate nurse liaison.

Patients (n=240) will be eligible to participate if they are on OST (ie, methadone); are aged at least 18 years; and attend the practice for any reason during the recruitment period.

Approach to Sampling and Recruitment

A standardized nonprobability sampling framework will be used to identify 10 consecutive patients from each practice or center to participate in the study. On the basis of the recommendations for good practice in feasibility studies [30] and our previous work conducting feasibility studies with PWID [29,31], we estimate that 240 patients (attending 24 general practices) will be adequate to calculate the actual recruitment and retention rates (ie, feasibility) and provide data on acceptability of study processes and outcome measures, which will inform a future definitive trial. This approach to recruitment reflects the challenges involved in recruiting this population group for projects. Patients who consult a doctor or nurse in participating practices or centers and who are eligible for the study will be given written information and a verbal explanation of the study, including the study purpose, procedures, and how findings will be utilized. Those who are interested in participating will be asked to sign a consent form, which will be witnessed by the doctor or nurse or the researcher. Although the initial approach to participate will be from a health care professional, recruitment will be facilitated by a member of the research team being “on site” to support the practice during the recruitment phase and

answer any questions potential participants may have. The recruitment phase will involve each participating practice engaging in an intensive, 4-week period of patient recruitment, an approach we found most effective in previous work with this population [28,29]. During this 4-week period, the member of the research team will aim to (1) obtain contact details for and informed consent from eligible patients, (2) review the clinical records of patients who consent to participate in the study, and (3) collect baseline data, including patient demographics and current care process and outcome measures from clinical records.

Intervention

Informed by the UK Medical Research Council “Framework for design and evaluation of complex interventions to improve health” [32], the aim of the intervention is to enhance identification and linkage to HCV care and treatment among patients attending primary care for OST and includes the following (see Figure 1):

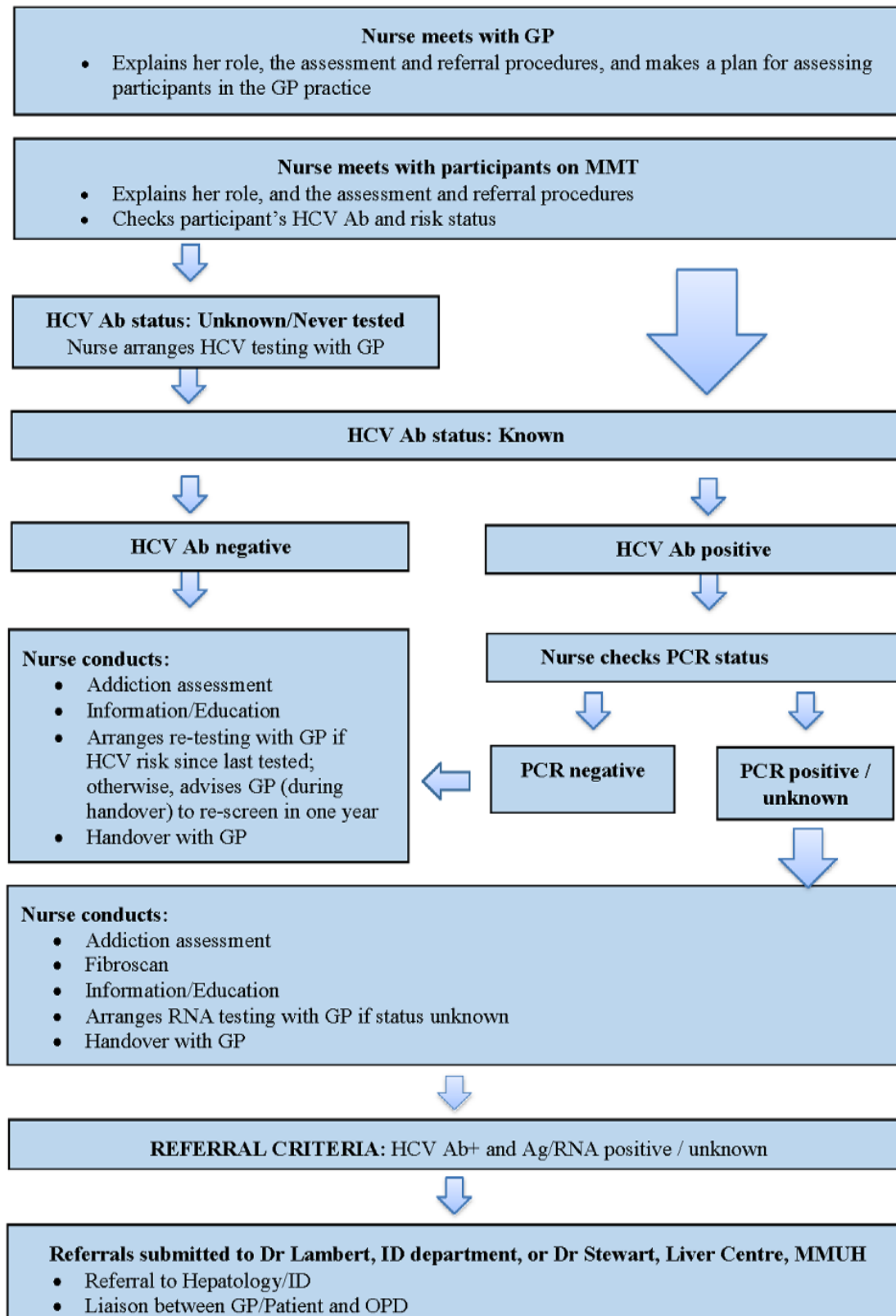
- Outreach of an HCV-trained liaison nurse into GP practices
- In-practice education for GPs and practice staff regarding developments in diagnosis and treatment of HCV
- Enhanced access of patients to community-based evaluation of HCV disease, including a novel approach to diagnosis, that is, transient elastography (Echosens FibroScan Mini 430)
- Researcher-facilitated practice audit of HCV care processes and feedback to GP

Data Collection

Data on patient demographics and HCV care processes/outcomes will be extracted from the patient’s clinical electronic or paper medical record and also from patient self-reported data collected through the HCV liaison nurse assessment to include the following:

- Prior HCV testing
- HCV status—antibody and Ribonucleic Acid (RNA) or antigen
- Referral and attendance for HCV care at a hospital’s Department of Hepatology or Infectious Diseases
- HCV assessment and treatment and sustained virological response (SVR)
- Alcohol screening and brief intervention using a validated alcohol screening instrument (eg, AUDIT)
- Other blood borne virus (BBV): HIV and hepatitis B virus (HBV)
- BBV testing/vaccination: liaison nurse will assess if the patient has been tested for HCV, HIV, and whether HBV immunization is required
- Chronic illness
- Mortality

Figure 1. Flowchart of the nurse-led intervention. GP: general practitioner; HCV Ab: HCV antibody; HCV: hepatitis C virus; ID: infectious diseases; MMUH: Mater Misericordiae University Hospital; PCR: polymerase chain reaction; OPD: Outpatient Department; OST: opiate substitution therapy; RNA: Ribonucleic Acid; Ag/RNA: Antigen/Ribonucleic Acid.



The HCV liaison nurse will meet and assess the patient, addressing any questions they may have regarding their HCV status. The liaison nurse will also gather data on the following variables:

- HCV risk factors (eg, incarcerated, tattoos, piercings, blood transfusion, sexually transmitted infection test)
- OST treatment
- Alcohol use assessed using the AUDIT questionnaire

- HCV testing, assessment, and treatment history
- Other BBV testing and HBV and hepatitis A virus vaccination history
- Quality of life (EQ5D-3L)—collected by HCV liaison nurse just before their assessment and intervention where necessary with each patient
- HCV-antibody positive and Ribonucleic Acid/Antigen (RNA/Ag) status (positive or unknown)
- Echosens FibroScan Mini 430 data (the nurse will have received Echosens FibroScan Mini 430 training)

After the assessment, the liaison nurse will provide the patient with information/education regarding HCV, including how it is transmitted and how to prevent transmission. Harm reduction strategies will also be addressed if required. A handover of the nurse's assessment will be given to the GP. HCV Ab+ patients will be referred to specialist services if they are Ag+, RNA+, or if Ag and RNA status are unknown. This process will be carried out by the GP with the assistance of the HCV liaison nurse. Referrals are submitted to the hospital's Hepatology or Infectious Diseases department.

Qualitative Data Collection

Semistructured interviews will be conducted by a member of the research team with health care professionals (n=12) and patients (n=12; or until analytical saturation is reached) at follow-up, purposively sampled from recruited practices and patients. Interviews will be guided by an interview schedule informed by our previous feasibility study in Irish primary care [33], including participants' lived experiences of HCV including barriers and facilitators to treatment, as well as questions exploring participants' experiences and acceptability of the study intervention. With purposive sampling, the researcher samples particular settings, persons, or events deliberately selected for the important information they can provide that cannot be acquired as well from other choices [34]. In line with the simultaneous analysis and collection of data that is an integral part of qualitative analysis, after the first 3 health care professional and first 3 patient interviews, recruitment will be informed by themes identified in the data. Participants recruited for the qualitative data collection will be provided with an amended participant information leaflet outlining the purpose of this part of the study, and, if agreeable, asked to sign a separate consent form.

Outcome Measures

To establish the feasibility, acceptability, and likely efficacy of this intervention in practice, the following outcome measures will be examined (see Table 1 for measures to establish feasibility, acceptability, and likely efficacy):

Primary outcomes include the following:

- Proportion of participants who have been screened for HCV
- Proportion of HCV antibody-positive patients commenced on/completed antiviral therapy/achieved SVR

Secondary outcomes include the following:

- Proportion of those screened who tested HCV antibody positive

- Proportion of HCV-positive patients who have been assessed by Echosens FibroScan Mini 430
- Proportion of HCV-positive patients who have been referred to specialist hepatology or infectious diseases service
- Proportion of HCV-positive patients who have attended specialist hepatology or infectious diseases service
- Proportion of HCV-positive patients received an alcohol screening brief intervention
- Proportion of participants tested for anti-HIV antibody, anti-HBc (hepatitis B core) antibody, or hepatitis B surface antigen (HBsAg)
- Proportion of participants immunized against hepatitis B/A virus
- Experience and evaluation of the intervention among key informants (GPs, nurses, and patients)
- Number of patients attending general practice for OST postintervention for follow-up testing
- Evaluate feasibility and possible efficacy of intervention by comparing pre-post intervention data
- Evaluate the cost-effectiveness of the intervention
- Compare GPs' and practice nurses' knowledge and attitudes and practice pre-post intervention

Data Analysis

Quantitative data will be analyzed using SPSS v22. Questionnaires will be summarized using descriptive statistics, and a pre-post intervention analysis will be performed using Fisher exact test.

Semistructured interview transcripts will be checked for accuracy and then imported into NVivo10 qualitative data analysis software to aid management and analysis of data. Analysis will begin shortly after data collection starts and will be ongoing and iterative. Analysis will inform further data collection; for instance, analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guide during later interviews. Thematic analysis [35] using a data-driven inductive approach will be used to scrutinize the data to identify and analyze patterns and themes of particular salience for participants and across the dataset. The first author (a social psychologist with extensive experience in using qualitative methodologies) will analyze and code the data. The data will also be independently analyzed by the second author who also has extensive expertise in qualitative research. Final themes will be agreed between the 2 authors, and the last author will audit the final analysis.

The goals of this study are to examine feasibility, acceptability, and likely efficacy of the intervention. Descriptive statistics will be analyzed with respect to key feasibility variables. The qualitative analysis of patients' and health care professionals' experiences of the intervention will be used to assess acceptability. Although the study is not designed to determine effectiveness, we will examine likely efficacy by comparing process and outcome measures, which will allow estimation of the intraclass correlation coefficient and thus inform the sample size of a possible future definitive trial.

Table 1. Measures to establish feasibility, acceptability, and likely efficacy.

Aim	Patient level	Practice level
Feasibility	Compare pre-post intervention data on patient demographics, hepatitis C virus (HCV) care processes and outcomes extracted from patients' clinical electronic or paper medical records, and also from patient self-reported data collected through the HCV liaison nurse assessment; patient recruitment rates; patient retention level; and cost-effectiveness of the intervention	Compare pre-post intervention data on patient demographics, HCV care processes and outcomes extracted from patients' clinical electronic or paper medical records, and also from patient self-reported data collected through the HCV liaison nurse assessment; practice recruitment rates; practice retention level; cost-effectiveness of the intervention
Acceptability	Patients' experience of intervention evaluated by analysis of semistructured interviews with patients	GPs ^a and practice nurses' experience of intervention evaluated by analysis of semistructured interviews with patients
Likely efficacy	Although not adequately powered to examine efficacy, possible efficacy will be assessed by proportion of patients who have been screened for HCV and alcohol use, proportion of patients who have been referred for treatment (HCV, alcohol), and cost-effectiveness of study	Although not adequately powered to examine efficacy, possible efficacy will be assessed by knowledge and attitudes and practice pre-post intervention and cost-effectiveness of study

^aGP: general practitioner.

Cost-Effectiveness

A cost-effectiveness analysis will be undertaken of the Heplink intervention. This analysis will be important to investigate whether this HCV case-finding intervention is a worthwhile investment.

Costs for the intervention will be collected (in Euros) from the provider's perspective using an ingredients-based approach, including a time and motion study of the nurse liaison activities. Health-related quality of life information will be collected using the EQ5D-3L (to calculate QALYs) at the start of the intervention, as there is a paucity of information for this patient group, with further quality of life data coming from other ongoing studies by the team. Using collected cost data and outcome data from the intervention, the long-term health benefits and costs of the intervention compared with the current standard of care will be calculated using a transmission dynamic model of HCV infection and disease progression. Further data to parameterize the model (PWID epidemiological and behavioral data and HCV transmission and progression data) will come from the published and gray literature. The incremental cost-effectiveness ratio will be calculated in terms of incremental cost per QALY saved and compared with the willingness-to-pay threshold for each country (€45,000 per QALY for Ireland) to determine whether the intervention is cost-effective.

Ethical Considerations

The study has been approved by the Mater Misericordiae University Hospital Research Ethics Committee (Ref: 1/378/1722) and the Research Ethics Committees of the collaborating institutions in London and Seville.

Ethical considerations and safeguards include the following:

- **Informed consent and consenting capacity:** all potential participants (GPs, patients) will be given written information on the study, the model of care being proposed, and asked to provide written consent that they are happy to participate and that nonparticipation will not compromise their usual care. Participation in the study will be on a voluntary basis. No inducements to participate will be offered.

- **Confidentiality:** Any data/personal details that could potentially reveal the identity of individuals will be removed. Only anonymized, deidentified information will leave the practice of origin. To allow follow-up, an alphanumeric code will be assigned to each participant's data; a database will be maintained on a password-protected database at Mater Misericordiae University Hospital. The list will be kept separately from patient data but will indicate the medical record number of each participant and the alphanumeric code. All research data will be stored on a password-protected desktop computer at the host organization. Study participants will be invited to give permission to have their name, address, and contact details held by the research team to facilitate their receiving a synopsis of the study findings on publication and to be contacted for follow-up data collection. All data will be stored securely at the host institution.
- **Clinical governance, do no harm:** it is possible that participating in the study may raise health-related issues for participants and may identify a health issue that requires a clinical intervention. Therefore, all participants will be advised to speak with their doctor if participating in the study has raised any such issues. At the conclusion of the intervention, the HCV-trained liaison nurse will conduct a handover of clinical information to the GP, which includes recommendations for follow-up care.

Results

The 3-year project is funded, from June 2016, by the European Union Third Health Programme (grant agreement number 709844) and Ireland's Health Services Executive. Data collection will be completed by July 2018, and data analysis is currently ongoing, with the findings expected to be submitted for publication in late 2018. Baseline data results from the Dublin arm of the study were submitted for publication in March 2018. The study findings have the potential to make an important impact on patient care and provide high-quality evidence to help GPs make important decisions on HCV testing and onward referral.

Discussion

Strengths and Limitations

“Heplink” is the first study to examine the feasibility and acceptability of integrated HCV care among problem drug users attending primary care in Europe. It will provide key data to enhance scientific understanding of interventions that prevent risk behaviors, inform policy and service development, and contribute to health and social gain locally and internationally. This study has the potential to make an important impact on patient care and will provide high-quality evidence to help GPs make important decisions on HCV testing and onward referral. The intervention is scalable and, therefore, if found to be feasible, acceptable, and cost-effective, it can be readily implemented elsewhere and used to guide policy and service development internationally.

Possible limitations of the study include potential issues of bias and lack of generalizability that may arise from the recruitment process, resulting in the likelihood that GPs who are more motivated and interested in research and innovation will choose to participate. Although target patient sample of 240 patients is

relatively small for a trial study, it will allow us to estimate the sample size required for a future definitive trial.

The project team involves academic, clinical, and policy experts responsible for planning and delivery of addiction care and primary care and international experts on optimum primary care delivery to at-risk populations and primary care alcohol treatment.

The proposed work builds on our previously conducted work that outlined the barriers and enablers to HCV screening and treatment in practice and examined the effectiveness of a nurse-led intervention to enhance HCV screening in primary care [36].

Conclusions

At the end of this research, the feasibility of a clinical intervention, informed by international best practice and local barriers, will be evaluated among a high-risk population. This feasibility study will inform clinical practice by providing initial indications as to whether a nurse-led integrated model of HCV care is feasible, acceptable, and also effective among problem drug users attending primary care. It will also inform future research on the topic by providing key parameters for the design of a future cluster randomized controlled trial.

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Authors' Contributions

GM led the development of the protocol with other coauthors contributing specific components. WC is the principal investigator and conceived the study. GM and WC led preparation of the manuscript with a core group of authors. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AUDIT: Alcohol Use Disorders Identification Test

BBV: blood borne virus

GP: general practitioner

HBV: hepatitis B virus

HCV: hepatitis C virus

OST: opiate substitution therapy

PAU: problem alcohol use

PWID: people who inject drugs

QALY: quality-adjusted life year

RNA: Ribonucleic Acid

SVR: sustained viral response

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Protocol

Relationship Between *Staphylococcus aureus* Carriage and Surgical Site Infections Following Total Hip and Knee Arthroplasty in the South Asian Population: Protocol for a Prospective Cohort Study

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Abstract

Background: Surgical site infections following total hip or knee arthroplasties have a reported rate of 0.49%-2.5% and can cause significant morbidity as well as tripling the cost of health care expenses. Both methicillin sensitive and methicillin resistant strains of *Staphylococcus aureus* surgical site infections have been established as a major risk factor for postoperative surgical site infections. *S. aureus* colonizes the nose, axillae, and perineal region in up to 20%-30% of individuals. Although the literature has reported a higher prevalence of methicillin resistant *S. aureus* in the South Asian population, routine preoperative screening and prophylaxis have not yet been implemented.

Objective: The primary objective of our study is to identify the relationship between preoperative colonization status of *S. aureus* and incidence of postoperative surgical site infections in patients undergoing following total hip and knee arthroplasties. As part of the secondary objectives of this study, we will also investigate patient characteristics acting as risk factors for *S. aureus* colonization as well as the outcomes of total hip and knee arthroplasty patients which are affected by surgical site infections.

Methods: This prospective cohort study will comprise of screening all patients older than 18 years of age admitted to the Aga Khan University Hospital for a primary total hip or knee arthroplasty for preoperative colonization with *S. aureus*. The patients will be followed postoperatively for up to one year following the surgery to assess the incidence of surgical site infections. The study duration will be 2 years (March 2018 to March 2020). For the purpose of screening, pooled swabs will be taken from the nose, axillae, and groin of each patient and inoculated in a brain heart infusion, followed by subculture onto mannitol salt agar and sheep blood agar. For methicillin resistant *S. aureus* identification, a cefoxitin disk screen will be done. Data will be analyzed using SPSS v23 and both univariate and multivariate regression analysis will be conducted.

Results: Data collection for this study will commence at the Aga Khan University Hospital, Pakistan during March 2018.

Conclusions: This study will not only estimate the true burden caused by *S. aureus* in the population under study but will also help identify the patients at a high risk of surgical site infections so that appropriate interventions, including prophylaxis with antibiotics such as muciprocin ointment or linezolid, can be made. Given the differences in lifestyle, quality, and affordability of health care and the geographical variation in patterns of antibiotic resistance, this study will contribute significantly to providing incentive for routine screening and prophylaxis for *S. aureus* including methicillin resistant *S. aureus* colonization in the South Asian population.

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KEYWORDS

Staphylococcus aureus; Staph aureus; orthopedic surgery; surgical site infection; SSI; infections

Introduction

Background and Rationale

Although orthopedic surgeries are generally classified as clean, with strict aseptic techniques and antimicrobial prophylaxis commonly being employed, surgical site infections (SSIs) continue to be a critical complication. Several studies have reported high surgical site infection rates ranging from 0.49% up to 2.5% following hip and knee arthroplasties [1-8]. Although rare, the cost of an SSI to both the patient and the health care system is tremendous. By prolonging hospital stay by a median of 2 weeks, SSIs cause significant morbidity, and with the added rehospitalization costs, they can more than triple overall health care expenses [9].

Needless to say, the prevention of SSIs requires identification of risk factors with appropriate interventions [10]. *Staphylococcus aureus* is a major pathogen which colonizes the nose, axillae and perineal region in up to 20%-30% of individuals [11-15], with the most established risk factor for colonization being the extremes of age [16,17]. The association between *S. aureus* carrier status with an increased risk of *S. aureus* infections was first recorded by Danbolt in 1931 [18]. It has been shown that carriers of *S. aureus* are 2 to 9 times more likely to acquire *S. aureus* SSIs than noncarriers [19-21]. In fact, a study has shown that nasal carriage was the only independent risk factor found for *S. aureus* SSIs in patients undergoing orthopedic implant surgery [5]. Furthermore, in patients who acquire *S. aureus* SSIs, paired *S. aureus* isolates from the wound match those from the nares 85% of the time [22]. Additionally, and more importantly, methicillin resistant *Staphylococcus aureus* (MRSA), a variant of *S. aureus* which is becoming an increasingly common pathogen, constitutes 2.58% of *S. aureus* isolates. MRSA colonization has been found to be associated with worse clinical outcomes after surgery and higher rates of mortality [23].

It has been reported previously that preoperative identification and decolonization with mupirocin ointment decreased the risk of staphylococcal infections from 2.6% to 1.5%. In addition to this, the number of non-staphylococcal infections is also decreased [24].

Knowledge of geographical variation in antibiotic resistance patterns is not new. Studies have reported a higher prevalence of MRSA in South Asian countries, approximately as high as 10.7%-19.51% [25-27]. However, the results of our hospital data from the past two years show a total of 3 SSIs following knee arthroplasty, none of which were caused by *S. aureus* [28]. This data suggests that *S. aureus* may not be the priority concern when it comes to SSIs following knee arthroplasties in our population. Given the resource limitation and fee for service policy in this part of the world, it is best to focus prophylaxis on the organisms shown to be responsible for SSIs in our data, such as gram negative bacteria. Therefore, this study will play a role in establishing whether *S. aureus* is truly a major concern in this population and whether it is cost effective to make it the

primary target for prophylactic therapies. The aim of our study is to estimate the incidence of SSIs caused by *S. aureus* and the prevalence of methicillin sensitive *Staphylococcus aureus* (MSSA) and/or MRSA colonization in the population presenting for elective orthopedic surgeries. To our knowledge, similar studies have not been conducted in the South Asian population and we hope that the results from our study will allow for appropriate interventions to be sought and implemented to promote superior health care practices for all.

Objectives

Primary Objective

The primary objective of this study is to determine the relationship between preoperative colonization of the nose, axillae, and groin by MSSA and/or MRSA and postoperative SSIs by MSSA and/or MRSA following elective total knee or hip arthroplasties.

Secondary Objectives

The secondary objectives of this study are listed below.

1. To estimate the incidence of surgical site infections caused by MSSA and/or MRSA following elective total hip or knee arthroplasty.
2. To identify patient characteristics associated with MSSA and/or MRSA colonization.
3. To evaluate the outcomes of total hip or knee arthroplasty in patients who are preoperatively colonized with *S. aureus* and postoperatively have an SSI with MRSA and/or MSSA.

Methods

Study Design

In this prospective cohort study, over the course of a year, patients admitted to a single tertiary care hospital for an elective total hip or knee arthroplasty will be screened for preoperative colonization with *S. aureus* (MRSA and/or MSSA). Postoperative follow-ups with these patients will then occur for up to one year to assess and document SSIs, among other outcome variables.

Setting

The study will be conducted at the Aga Khan University in Pakistan over a period of 2 years beginning March 2018. The expected completion date of the study is March 2020. Screening will be conducted for all patients admitted during the first year. The next year will be utilized to complete the one year of follow-up of each patient.

Participants

Inclusion Criteria

The inclusion criteria for participants in this study are as follows:

- All patients admitted for an elective total hip arthroplasty.
- All patients admitted for an elective total knee arthroplasty.
- Patients older than 18 years of age.

Exclusion Criteria

The exclusion criteria for participants in this study are as follows:

- Patients with history of MRSA infections in the last one month (based on culture positivity or having received treatment for MRSA).
- Patients undergoing revision arthroplasty.

Sample Size

We used Sample Size Determination in Health Studies (Version 2.0, 1998, WHO) to apply a formula for hypothesis testing using relative risk in cohort studies. In a previous study, Prince et al reported that the rate of infection in colonized groups is 4.7%, while it is 1% in noncolonized groups [15]. Thus, assuming the rate of infection in the colonized group is 4.7% versus 1% in the noncolonized group, we take the value of the relative risk due to colonization to be 4.7% with a level of significance at 5% and power of 0.9. This calculation showed the need for a minimum sample size of 423 subjects. Therefore, we intend to recruit 500 subjects to account for the losses in follow-up.

Variables

Both independent and dependent variables, as well as potential confounders, will be recorded in this study. The independent variable in this study is the carrier status of the patient, either positive (carrier of MRSA or MSSA or both) or negative.

The dependent variables in this study are as follows: surgical site status (infected or not), postoperative length of hospital stay (prolonged or not), postoperative complications (yes or no), and rehospitalizations due to surgical site infection (yes or no). A prolonged hospital stay will be defined as >1 SD from the mean hospital stay calculated for total hip or knee arthroplasties in our sample.

Potential confounders identified in this study are as follows: patient's sex (male or female), age at operation (≥ 65 years or <65 years), body mass index (≥ 30 kg/m² or <30 kg/m²), comorbid conditions (yes or no), type of procedure (hip vs knee), duration of surgery (prolonged vs non prolonged), American Society of Anaesthesiologist's status (≥ 3 or <3), previous hospital admissions within 6 months (yes or no), and antibiotic therapy within one month of current admission (yes or no). A prolonged duration of surgery will be defined as >1 SD from the mean duration of surgery calculated for total hip or knee arthroplasties in our sample.

Data Sources and Collection

Patients eligible to participate in the study as per the inclusion and exclusion criteria will be approached by 2 trained researchers, 1 male and 1 female, at their respective beds in the wards on the day of admission, prior to the commencement of standard preparation for surgery. The researchers will explain the purpose and procedure to them in the local language and obtain consent. They will provide a written consent form (Multimedia Appendix 1) which the patients will be asked to sign if they accept the invitation to participate in the study. If any patient is unable to consent for themselves for reasons including, but not limited to, cognitive impairment or physical

incapacitation, consent will be obtained from the health care proxy as applicable. During this first interaction with the patient, samples will be taken and sent to the microbiology lab to determine colonization, if any, by *S. aureus* (details of sample collection are described below) and all questions pertaining to the patient's demographics and preoperative characteristics will be recorded in the questionnaire (Multimedia Appendix 2). The patient will undergo the planned surgery the following day. Postoperatively, the patient's medical record files will be used to document the details of the surgical variables relevant to this study. As per guidelines for arthroplasties, all patients receive a cefazolin dose intraoperatively and 3 doses postoperatively. Any variations in this regimen will be noted and included in the analysis.

Patient Follow-up

Follow-ups of patients included in this study will be conducted via phone calls made by the research officer at 2 weeks, 2 months, 3 months, 6 months, and 1 year after discharge from the hospital stay following the initial surgery. If any symptoms reported by the patients are suspicious, they will be advised to visit their primary physician for a follow-up where documentation of an SSI will occur using the criteria listed below. Following examination, if an infection is suspected, attending surgeons will be encouraged to send samples from the surgical site to culture so identification of MSSA and/or MRSA can be conducted. Patients lost to follow-up will be excluded from the analysis.

Study Outcome Definition

Diagnosis of an SSI will be based on the criteria put forward by the Centers for Disease Control and Prevention [10]. An SSI will be classified into one of 3 groups listed below.

1. Superficial incisional surgical site infection occurring within 30 days of surgery.
2. Deep incisional surgical site infection.
3. Organ or space surgical site infections occurring within 30 days of surgery if no implant is left in place or within 1 year if the implant was in place and the infection appeared to be related to the surgery.

All pathogens will be examined for all SSI cases. An SSI with MRSA will be assessed using the same culture method as used for assessment of nasal MRSA.

Sample Collection

For the purpose of screening for MRSA or MSSA, pooled swabs will be taken from the nose, axillae, and groin of each patient. A total of 3 transport swabs will be used for each patient, one for both nares, one for both axillae, and one for the bilateral groin region. For adequate sampling, each swab will be rubbed for a total of 5-6 seconds in each region. Three transport swabs for each patient will be labelled with a single code and transported to the microbiology lab for further processing.

Laboratory Procedure

Pooled swabs from each patient will be inoculated in a brain heart infusion for 24 hours at 37 C, following which the specimen will be subcultured onto mannitol salt agar and sheep blood agar. The agar plates will be assessed after 24 hours. For

none or minimal growth, the plate will be reincubated and reassessed at 48 hours. *S. aureus* will be identified by tube coagulase and deoxyribonucleic acidase production. For MRSA identification, a cefoxitin disk screen will be conducted.

Statistical Analysis

Patients admitted several times during the study period will be included only once in the analysis. Data will be analyzed using SPSS v23. The Shapiro-Wilk Test will be used to assess normality of the variables. For normally distributed data, means will be reported and comparison will be done using a *t* test or Wilcoxon signed rank test. For skewed data, medians with interquartile ranges will be reported and comparisons will be conducted using the Mann-Whitney *U* test. For categorical variables, we will use a chi-square test for comparison. If chi square assumptions are violated, the Fisher exact test will be used. In addition, a Kaplan-Meier survival analysis will be used to compare the two groups; the patients who were tested positive for MRSA or MSSA colonization and patients who were negative for MRSA or MSSA colonization.

Multiple logistic regression analysis will be performed to estimate adjusted relative risk (odds ratios, ORs) and their 95% CIs. For univariate testing, the threshold for qualifying for further analysis will be *P* value <0.20. All variables with *P* values <0.05 in multivariate regression analysis will be declared significant. The test for trend will be performed by including explanatory variables in the model that will be coded by ordinal numbers with increasing categories of exposure.

Ethical Approval

Approval for the conduction of this study has been taken from the Ethical Review Committee (ERC) of Aga Khan University Hospital, Pakistan; ERC Number: 4014-Sur-ERC-16.

Results

Data collection for this study will commence at the Aga Khan University Hospital, Pakistan, on March 5, 2018.

As part of the primary objective and secondary objective three, we will demonstrate the relationship between the preoperative carrier status (independent variable) and postoperative SSI (dependent variable for the primary objective) and other dependent variables as a crude and adjusted relative risk (RR), as shown in example [Multimedia Appendix 3](#).

As part of secondary objective two, we will demonstrate the relationship between the carrier status (independent variable) and potential confounding variables as both crude and adjusted ORs, as shown in example [Multimedia Appendix 4](#).

Discussion

Principal Results

The South Asian population belongs to the developing world. Together with the differences in lifestyle, quality of health care, and the affordability of health care expenses, the geographical variation in patterns of antibiotic resistance makes it imperative to study the incidence of SSIs caused by *S. aureus*, particularly MRSA, with emphasis on the relationship between preoperative

colonization and postoperative infections. This will not only help to identify the patients at a high risk of SSIs, but also allow the staging of appropriate interventions, such as prophylaxis with an antibiotic which provides MRSA coverage (eg, mupirocin ointment).

Although no study investigating the relationship between preoperative colonization and postoperative infection by *S. aureus* for orthopedic surgeries has been conducted in our region where the aseptic measures may be stricter, similar studies in other regions have been conducted in the past. In 2001, Ziaullah et al reported that out of 308 hospital personnel, 20.8% were found to be nasal carriers of *S. aureus*, with MRSA accounting for 10.7% of the samples [27]. In 2014, Anwar and colleagues reported that out of 1660 nasal samples taken from patients' attendants, a total of 246 (14.82%) samples were positive for growth of *S. aureus*. Out of the 246 positive samples, 48 (19.51%) isolates were MRSA [26]. In the same year, Khurram et al reported that out of 1431 patients admitted in the ICU, 57 patients developed infections with MRSA. They showed that older (>52 years), diabetic patients with a central venous line in place were at a significantly higher risk of developing these infections [29]. The report also showed that the rate of surgical site infection following clean cardiovascular surgery was 4%; 40% of which was caused by *S. aureus* [29].

Our study aims to investigate the relationship between preoperative colonization and postoperative infections by *S. aureus*. Although this study does justice to the defined objectives within the scope of resources available to us, the elaboration of certain issues and relevant recommendations may help in drawing stronger conclusions from future studies.

The methodology described will accurately depict a correlation between preoperative carrier status and postoperative infection by *S. aureus*. However, in order to establish a causal relationship between the two variables, the *S. aureus* strains need to be typed (eg, by pulse field gel electrophoresis) [30]. The recommendations to administer antibiotic prophylaxis with MRSA coverage could nevertheless still be made if the incidence of postoperative MRSA infections was found to be significant. In addition to preoperative cultures, intraoperative and postoperative cultures, together with cultures at regular follow-up intervals, can be planned for future studies to account for acquisition of *S. aureus* during and after the surgical procedure.

In our study, we are using pooled swabs from the nose, axillae, and groin cultured together to establish the carrier status. Although culturing the sample from each region separately would increase the cost, it would allow us to identify the most common area for colonization by *S. aureus*. This may impact the choice of agent to be used as antibiotic prophylaxis since mupirocin ointment applied locally for intranasal colonization has been a popular choice, but its application over large areas increases its resistance [17]. So, if the axillae and groin were also found to be colonized, systemic antibiotics such as linezolid could be considered as an alternative [31]. Furthermore, quantification of culture results could also aid in the making the decision between local and systemic antibiotics.

The methodology described in our study for the follow-up of patients up to one year postsurgery has some limitations. Firstly, patients may acquire MRSA from subsequent hospitalizations other than those in our hospital following discharge and may be prescribed antibiotics for infections other than those of the surgical site during the one year of follow-up. Secondly, a long follow-up adds to the potential confounders which may influence the results. Therefore, we recommend a more thorough documentation of potential confounding variables and an elaborate analysis plan to take those factors into account to draw more robust conclusions from future studies.

Benefits and Potential Risks

The treatment plan for all patients will follow the standard protocol regardless of participation in the study. Specimen sample collection itself will take a maximum of 15 minutes of

the patient's time if they choose to participate. Results of a positive screening for MSSA or MRSA will be communicated to the patient via telephone, so they can use this information in any future surgeries they undergo.

Conclusion

This prospective cohort study will add to the current literature by investigating the relationship between preoperative colonization and the postoperative incidence of SSIs by MSSA and/or MRSA following orthopedic surgeries in the South Asian population. The study will allow for the identification of patients at a higher risk of developing an SSI so that appropriate interventions including local or systemic antibiotic prophylaxis can be planned. This may lead to a reduction in the rates of SSIs following relatively expensive surgeries and decreasing hospital costs for a population which belongs to the developing world.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Consent form.

[[PDF File \(Adobe PDF File\), 32KB - resprot_v7i6e10219_app1.pdf](#)]

Multimedia Appendix 2

Demographics and preoperative characteristics questionnaire.

[[PDF File \(Adobe PDF File\), 33KB - resprot_v7i6e10219_app2.pdf](#)]

Multimedia Appendix 3

Relative risk of each dependent variable with a positive carrier status for *S. aureus*.

[[PDF File \(Adobe PDF File\), 13KB - resprot_v7i6e10219_app3.pdf](#)]

Multimedia Appendix 4

The relationship between a positive carrier status of *S. aureus* and various patient characteristics.

[[PDF File \(Adobe PDF File\), 38KB - resprot_v7i6e10219_app4.pdf](#)]

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Abbreviations

- ASA:** American Society of Anesthesiologists
ERC: Ethical Review Committee
MRSA: Methicillin resistant *Staphylococcus aureus*
MSSA: Methicillin sensitive *Staphylococcus aureus*
OR: odds ratio
RR: relative risk
SSI: surgical site infection

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Protocol

Types and Frequency of Infusion Pump Alarms: Protocol for a Retrospective Data Analysis

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Abstract

Background: The variety of alarms from all types of medical devices has increased from 6 to 40 in the last three decades, with today's most critically ill patients experiencing as many as 45 alarms per hour. Alarm fatigue has been identified as a critical safety issue for clinical staff that can lead to potentially dangerous delays or nonresponse to actionable alarms, resulting in serious patient injury and death. To date, most research on medical device alarms has focused on the nonactionable alarms of physiological monitoring devices. While there have been some reports in the literature related to drug library alerts during the infusion pump programming sequence, research related to the types and frequencies of actionable infusion pump alarms remains largely unexplored.

Objective: The objectives of this study protocol are to establish baseline data related to the types and frequency of infusion pump alarms from the B. Braun Outlook 400ES Safety Infusion System with the accompanying DoseTrac Infusion Management Software.

Methods: The most recent consecutive 60-day period of backup hospital data received between April 2014 and February 2017 from 32 United States-based hospitals will be selected for analysis. Microsoft SQL Server (2012 - 11.0.5343.0 X64) will be used to manage the data with unique code written to sort data and perform descriptive analyses. A validated data management methodology will be utilized to clean and analyze the data. Data management procedures will include blinding, cleaning, and review of existing infusion data within the DoseTrac Infusion Management Software databases at each hospital. Patient-identifying data will be removed prior to merging into a dedicated and secure data repository. This pooled data will then be analyzed.

Results: This exploratory study will analyze the aggregate alarm data for each hospital by care area, drug infused, time of day, and day of week, including: overall infusion pump alarm frequency (number of alarms per active infusion), duration of alarms (average, range, median), and type and frequency of alarms distributed by care area.

Conclusions: Infusion pump alarm data collected and analyzed in this study will be used to help establish a baseline of infusion pump alarm types and relative frequencies. Understanding the incidences and characteristics of infusion pump alarms will result in more informed quality improvement recommendations to decrease and/or modify infusion pump alarms, and potentially reduce clinical staff alarm fatigue and improve patient safety.

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KEYWORDS

medical device; alarms; infusion pumps; alarm fatigue; patient safety

Introduction

Background

The high incidence of alarms in hospital settings presents a potentially serious problem for patients and caregivers. Between 1983 and 2011, the potential variety of medical device alarms proximate to an intensive care unit (ICU) bed increased from 6 to 40 [1]. Medical devices emitting these alarms include, but are not limited to, physiological monitors, ventilators, pulse oximetry machines, and infusion pumps. It has been reported that these devices share similar alarm volume characteristics that range between 58 and 85 decibels, which compete for clinician attention in patient settings with background noise ranging between 56 and 76 decibels [2,3]. Alarms may interfere with a patient's sleep, cause unnecessary anxiety, and potentially negatively impact healing [4,5].

Eighty to 99% of medical device alarms are generally thought to be clinically insignificant and/or require no intervention. These nonactionable alarms include those emitted from physiological monitors when parameter thresholds are set too narrowly, causing clinically insignificant alarms to occur [5,6]. It has been suggested that the abundance of nonactionable alarms results in desensitizing clinical staff to all alarms, in turn affecting response time to those that are actionable [5,7,8]. This desensitization, commonly described as alarm fatigue, is an increasingly critical safety issue that can lead to potentially dangerous delays or nonresponse to actionable alarms, which require clinical staff intervention to resolve.

In an effort to reduce patient risk associated with alarm fatigue, alarm management has become a priority issue for national guidance organizations, including The Joint Commission, the Food and Drug Administration, the Association for Advancement in Medical Instrumentation, Emergency Care Research Institute (ECRI), and the American College of Clinical Engineering Healthcare Technology Foundation. In 2016, ECRI listed clinical staff alarm desensitization as a top 10 health technology hazard, stating that fatigue due to the high incidence of nonactionable alarms could result in missed, actionable ventilator alarms that require clinician intervention [9]. The Joint Commission [10] also listed alarm management as a National Patient Safety Goal, stating in 2018 that quality improvements must be made to ensure timely clinical alarm response time. While national guidance organizations have established goals to reduce patient risk through more effective clinical alarm management in general, no research has been conducted to benchmark alarm data to inform specific quality improvement recommendations for infusion pumps specifically [4,8,9,11].

The current evidence related to the incidence of nonactionable and actionable medical device alarms and their associated impact on the desensitization of clinical staff is limited. Research has primarily focused on electrocardiograms (ECGs), physiologic monitors, and pulse oximetry in the telemetry and ICUs, where the total alarm incidences of these devices is thought to be highest [1,5,12]. Alarm incidence in the ICU has been reported as high as 45 times/patient/hour [1], of which 77% are ineffective and/or ignored [13]. Interventions to mitigate

nonactionable alarms, including better ECG electrode placement, adjusting alarm thresholds, and education on monitor capabilities and alarms, have resulted in a 12% to 89% reduction in these types of alarms [4,6,7,14-18].

The recommendations to reduce the nonactionable alarms of physiologic, ECG, and pulse oximetry monitors are not applicable to infusion pumps. Most infusion pump alarms are actionable; that is, they continually alarm until addressed by clinical staff. Infusion pump alarms have been found to contribute to 10% to 12% of total ICU alarms with 0% of these alarms being ineffective [1,13]. However, compared to other medical device alarms, infusion pump alarms can last longer [13] and may account for approximately 5% of the infusion time [19]. The differences between high-proportion, nonactionable physiological monitoring alarms and the low-proportion, actionable alarms of infusion pumps require an investigation to study the specific types and frequencies of infusion pump alarms. It is important to note the difference between infusion pump "alarms" and "alerts." While there has been a concerted effort to aggregate data related to smart pump programming dosing alerts in order to measure impact on drug library compliance [20], the clinical and caregiver impact of postprogramming infusion pump alarms remains largely unexplored. For the purpose of this study, an infusion pump alarm is defined as an audible and visual signal during pump operation that requires the user to address/resolve to silence the alarm.

Before making recommendations to decrease or modify what are believed to be mostly actionable alarms, understanding the incidences and characteristics of infusion pump alarms is necessary. Ultimately, benchmarking the incidences and characteristics of infusion pump alarms will lead to more informed quality improvement recommendations to decrease and/or modify infusion pump alarms while both reducing clinical staff alarm fatigue and maintaining patient safety.

Objectives

The primary objective of this study is to establish baseline data related to the types and frequency of infusion pump alarms from the B. Braun Outlook 400ES Safety Infusion System with DoseTrac Infusion Management Software. Alarm type, duration, day of week, time of day, drug name, care area, number of deliveries, and number of pumps in use will be captured and evaluated to determine if alarm types and frequency differ according to hospital/unit and, if so, suggest what factors may contribute to these differences.

Methods

Study Design

This retrospective study [21] will describe the types and frequency of alarms that occur during infusions with the B. Braun Outlook 400ES Safety Infusion System via DoseTrac at 32 hospitals collectively using approximately 13,000 large volume infusion pumps (April 2014 to February 2017). The DoseTrac application resides on each hospital's server, and holds up to 18 months of data, with the ability to automatically back-up unlimited amounts of data in a separate file. We will

utilize back-up copies of this data previously obtained for analytic services and the most recent consecutive 60-day period will be selected for analysis and summarized using descriptive statistics. The majority of the hospitals (n=28) are located on the East Coast (Pennsylvania, New Jersey, New York, Maryland, Virginia, North Carolina, and Florida); the others (n=4) are located in Kentucky, Iowa, and California.

Investigational Infusion Device

The B. Braun Outlook 400ES Safety Infusion System is an electrical, external, large volume pump intended primarily for use in hospital, ambulatory, and/or extended care settings. The pump is intended for use with adult, pediatric, and neonatal patients and is equipped with distinct audible and visual alarm signals to indicate Keep Vein Open (KVO), low battery, and other alarm conditions [22]. This pump's system can customize up to 300 drugs and 15 care areas. The system provides for 2-way wireless communication allowing inbound receipt of drug library files and patient-specific infusion orders, along with outbound transmission of infusion data. The pump also includes a software application which collects, displays, and stores infusion data. The management and analysis of these data allows clinicians to continuously improve the quality and safety of intravenous (IV) infusion protocols. This software application consists of 3 components:

1. A real time infusion data collection service.
2. A database that stores up to 18 months of accumulated infusion data so that it can be displayed or reported in a useful way.
3. A Web application with:
 - i. Real-time remote views of active infusion pump status that is automatically updated every 5 seconds.
 - ii. Retrospective reports on various infusion metrics.
 - iii. A report scheduler that creates and saves reports/templates and schedules for email delivery [22].

Infusion data is automatically transmitted wirelessly from the pump across the hospital's secured wireless network and collected by the application for availability to both end users and other hospital information management systems. Authorized users can access the Web application from their secure hospital network computer by using the hospital's browser technology and entering their username and password. The database holds up to 18 months of data and has the ability for each hospital to automatically backup data on a daily basis.

Study Procedures

Participating hospitals transferred a database copy containing up to 18 months of infusion pump data to the investigator (April 2014 to February 2017) for periodic analytic services. Data was imported and sent via secure file transfer protocol (SFTP) to a secure central server protected by firewalls that are Health Insurance Portability and Accountability Act (HIPAA) deidentified (as necessary), and merged with a dedicated, secure data repository. A subset of these data containing a consecutive

60-day timeframe (ie, same quantity of days) for each hospital will be used in the statistical analyses.

The infusion pump has 11 types of alarms. A listing of alarms, associated cause(s), and effect(s) can be found in Table 1. All of the alarms produce an audible sound and visual signal on the pump screen indicating the type of alarm. All of the alarms are continuous and require clinician intervention to silence/resolve. Most of the alarms will stop the infusion or prevent it from being initiated until the alarm condition is resolved by the clinician.

Inclusion criteria

1. Hospitals that use one particular model pump (B. Braun Outlook 400ES Safety Infusion System) with the accompanying infusion management software (DoseTrac) and have agreed to the terms of a signed data licensing agreement, which allows the investigator access to infusion management software database data.
2. Pumps and infusion management software database data alarm records must include complete and consistent data elements to be included in the analysis. A complete alarm record will include all matching and consistent data elements from alarm start to alarm silence.

Exclusion criteria

1. Alarm records with potentially missing data resulting in incomplete records will be excluded. This includes records where an alarm is initiated with no accompanying end record, indicated by a hold state to silence and address the alarm, and any alarm record with data elements that differ at the start of the alarm from the end of the alarm (eg, drug name, concentration, rate, dose, VTBD, KVO volume does not equal zero, or different version of drug library) [23].
2. Alarm records associated with duplicate infusion pump serial numbers of "0" will be excluded from analyses. Infusion pump serial numbers can revert to "0" after major biomedical repairs. If the original pump serial number is not reentered, a hospital might have multiple pumps with a "0" serial number. As a result, the data from these "0" serial number pumps would appear to originate from a single device, while in actuality could result from a combination of data elements from multiple devices [23].

Data Collection

Each hospital periodically copies and transfers a back-up of software database data (containing up to 18 months of data) via SFTP to a central server for requested analytic services. Patient Personal Health Information is deidentified prior to inclusion into a secure data repository. Access to the secure database is secured by Citrix and Virtual Private Network passwords and is accessible by a single Information Technology (IT) administrator/investigator. The database is backed-up daily for both local and off-site storage. The IT administrator/investigator who manages the central data repository does not interpret the data.

Table 1. Infusion pump alarm types, associated cause(s), and effect(s).

Alarm Type	Cause	Effect
Air In Line	Air-in-line sensor at pump detects air in the intravenous (IV) tubing (eg, due to improper priming or venting of tubing, collection of micro bubbles, negative pressure and out gassing, residual air in container)	Pump infusion stops and alarms until user resolves
Bag Empty	Empty container; pump cannot pull from container	Pump infusion stops and alarms until resolves
Battery Empty	Battery power is nearly fully discharged with approximately 3 minutes remaining	Pump alarms until plugged into outlet or, if it reaches fully discharged battery state, the pump powers off and the infusion is stopped
Check Set	IV tubing improperly loaded into pump; free flow clip may not be fully engaged	Pump alarms and infusion cannot be initiated until user resolves
Door Open	Door is opened while infusing; pump was not put in hold prior to opening door	Pump infusion stops and alarms until user resolves
Downstream Occlusion	IV line is occluded below the pump (eg, lower roller clamped, tubing kinked, or IV catheter occluded)	Pump infusion stops and alarms until user resolves
Hold Time Exceeded	Hold time has been exceeded; user put pump on hold and did not restart infusion	Pump remains in hold state (not infusing) and alarms until user resolves
KVO (Keep Vein Open)	Programmed volume to be delivered (VTBD) has infused (has reached 0 mL)	Pump infusion rate decreases to 3 mL/hour (or if programmed rate is <3 mL/hour it will continue to infuse at same rate) and alarms until user resolves (put infusion on hold and program new VTBD)
Low Flow From Container	IV line is partially occluded above the pump (eg, upper roller clamp partially closed or tubing kinked)	Pump infusion stops and alarms until user resolves
System Error	Device requires reboot or service	Pump alarms (not infusing) and continues until powered off. If reboot (power cycle) does not resolve, then user must send the pump to biomedical engineering for service
Upstream Occlusion	IV line is occluded above the pump (eg, upper roller clamp closed or tubing kinked)	Pump infusion stops and alarms until user resolves

Since hospital alarm data are not currently preassembled into a standardized interface report on this version of software, it will be necessary to collate and assemble the data in a meaningful way, using a data assembly tool. Collating data across multiple hospitals and running queries on that data entails intricate manipulation of enormous amounts of complex data. Microsoft SQL Server (2012 - 11.0.5343.0 X64), a database that supports a mix of transaction processing, data warehousing, and analytics applications, will be used to help manage the data. Unique code will be written to sort the data to complete the descriptive analyses (percent, mean, median, mode, range, and frequencies, as appropriate). In addition, anticipating that there might be clinically nonsignificant alarm data in the database, a data cleaning process has been developed and tested to detect, diagnose, and edit out clinically nonsignificant data. The methodology to be used in this study for collating, cleaning, and assembling valid and reliable pump alarm data across multiple hospitals was previously reported [23].

Pump data are complex and potentially contain data falling within certain preidentified data exclusions. Only data that does not fall within the exclusion principles will be included in the analysis. Additionally, elements of the software management database data need to be combined to ensure capture of the particular information needed to answer our research questions. Individual hospital names will be visible only to investigators, as this is relevant to collating and comparing hospital metrics

(eg, census, staffed beds, case mix index), but will not be published.

Data Elements to be Analyzed

A subset of data collected between April 2014 and February 2017, which encompasses a consecutive/concurrent 60-day interval, will be selected from each hospital backup database and then analyzed as a combined group. If this is not possible, a consecutive 60-day timeframe will be used. Data elements to be analyzed from the software management database are listed in [Textbox 1](#).

Planned Statistical Analysis

The exact sample size for each data point/element was not statistically determined. The study will be exploratory in nature, thus the complete census of hospitals/pumps/alarm occurrences (minus those meeting the exclusion criteria) will be analyzed. Specific findings will be reported using the aggregate data for each hospital by care area, drug infused, time of day, and day of week, including: overall infusion pump alarm frequency (number of alarms per active infusion), duration of alarms (average, range, median), and type of alarms that occur in each hospital (percent breakdown of each type of alarm for each hospital). All data will be summarized and displayed in tables using descriptive statistics including mean, standard deviation, median, minimum, and maximum. Plots/graphs may also be used to summarize and display these data.

Textbox 1. Data elements that will be analyzed from the software management database. KVO: Keep Vein Open.

Facility Information
<ul style="list-style-type: none"> • Facility name • Number of hospital sites • Number of pumps purchased • Number of pumps in use • Pump “go-live” date • Number of licensed/staffed beds • Number of annual admissions • Case Mix Index
Data Per Alarm
<ul style="list-style-type: none"> • Date and time stamp (start and stop of alarm) • Pump serial number • Care Area (selected within drug library) • Location (if this feature used, unit or department name) • Mode (eg, primary, secondary, basic, drug library) • State (alarm, hold, run, KVO) • Drug name • Alarm type
Metrics
<ul style="list-style-type: none"> • Active delivery state: total time (minutes:seconds) and percentage of time pumps in hold, run, alarm, and KVO state; total time from “run” to “off” that a pump can alarm • KVO state: total time (minutes:seconds) and percentage of time pumps in KVO state • Alarm state: total time (minutes:seconds) and percentage of time pumps in alarm and KVO state • Alarm frequency by type: number of alarms that fall within each alarm type in the defined date range • Total deliveries: number of unique medication deliveries running in the defined date range • Average alarms per delivery: total number of alarms/total deliveries • Average alarm duration: cumulative duration (minutes:seconds) of all alarm states/total number of alarms • Total pumps available for analyses: number of unique pump serial numbers recorded in the defined date range

One-way analyses of variance (ANOVAs) will be used to determine any statistically significant differences between the hospitals, care areas, drugs, time of day, and day of week. Level of significance will be set at $P < 0.01$. If statistically significant overall differences are found between the various groups, appropriate post hoc tests will be conducted to determine specifically where the differences exist. If the data meet the assumption of homogeneity of variances, Tukey's honestly significant difference post hoc test will be used. If the data do not meet the homogeneity of variances assumption, the Games Howell post hoc test will be used.

Microsoft SQL Server (2012 - 11.0.5343.0 X64), a database designed to support a mix of transaction processing, data warehousing, and analytics applications, will be used to manage the data and unique code will be written to collate and assemble the data to complete descriptive analyses. Specific applicable files will be transferred to Statistical Package for the Social

Sciences Statistics version 22 (IBM-SPSS Inc, Armonk, NY) to complete the significance testing.

Ethical Considerations

This study will be conducted in full accordance with all applicable Federal and State laws and regulations, including 45 CFR 46 and the HIPAA Privacy Rule. Each hospital's alarm data will be blinded and cleaned prior to analysis. All patient-identifying data will be removed prior to merging into the dedicated and secure data repository.

To protect the integrity and security of the data, the infusion pump only uses one-way ports, meaning that data is transmitted only from the pump to external applications (eg, data management software). Data cannot be received by these outbound ports. The data management software port is also one-way, receiving inbound data only with a specific format, including a prefix, data, and checksum. Invalid incoming messages are rejected. The pump also utilizes a specific set of

encryption/authentication schemes to meet hospital network setting requirements. The outbound infusion data format is industry standard Health Level-7 messaging and Integrating the Healthcare Enterprise - Patient Care Device compliant. Infusion data are transmitted over the hospital network to the infusion management software. As outlined in the infusion management software schedule and software terms of use (internal documents), investigators have been authorized to use certain data stored by the software on a deidentified, aggregate basis. Institutional Review Board approval for this work was not sought as the study will not directly involve human participants.

Discussion

Potential Benefits to Patients

Alarms from all medical devices are either nonactionable or actionable. Alarms emanating primarily from physiological monitoring devices have a higher proportion of being nonactionable while infusion pump alarms are mostly actionable. Nonactionable alarms have been associated with increased clinical staff desensitization toward all types of alarms. The resulting alarm fatigue has been identified as a critical safety issue resulting in potentially dangerous delays or nonresponse to actionable alarms contributing to serious patient injury and death. To date, there have been very limited analyses to show how infusion pump alarms specifically contribute to alarm fatigue and impact patient care. If we can better determine the incidences and characteristics of infusion pump alarms we can begin to focus on potential pump and clinical workflow design

changes that prioritize rapid clinician response time for the actionable alarms required to ensure patient safety.

This study is designed to provide new insights regarding the prevalence and characteristics of infusion pump alarms related to the types and frequency of these alarms, including: alarm type, duration, day of week, time of day, drug name, care area, location, number of deliveries, and number of pumps in use. The benchmarking of this data, in addition to the analysis of the consistencies and inconsistencies of alarm types and frequencies between hospitals and hospital units, will help lay the foundation for future research initiatives, ultimately resulting in a decrease in alarm fatigue and better patient care and outcomes.

Strengths and Limitations

This study will be an important first step in benchmarking types and frequencies of infusion pump alarms. However, the resulting data analysis will be limited since it will only include datasets from hospitals that use one particular large volume pump and its associated infusion management software, and have agreed to participate in the study by signing a data licensing agreement that allows investigator access to their infusion source data. In addition, datasets will vary in size (number of months) and may vary based upon time of year (in the event the analysis of concurrent datasets is not possible). Analyzing the same total number of months (ie, last 60 days of data available for each hospital site) will result in a comprehensive alarm data set, but this analysis will not include variables that could impact results like equality in time of year, pumps per patient ratio, or patient acuity.

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Conflicts of Interest

All authors certify that they have no affiliations with, or involvement in, any organizations or entities with a financial interest beyond their full-time employment at B. Braun Medical Inc.

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Abbreviations

ECG: electrocardiogram
ECRI: Emergency Care Research Institute
HIPAA: Health Insurance Portability and Accountability Act
ICU: intensive care unit
IT: information technology
IV: intravenous
KVO: Keep Vein Open
SFTP: secure file transfer protocol
VTBD: volume to be delivered

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Protocol

INTERGROWTH-21st Gestational Dating and Fetal and Newborn Growth Standards in Peri-Urban Nairobi, Kenya: Quasi-Experimental Implementation Study Protocol

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Abstract

Background: The burden of preterm birth, fetal growth impairment, and associated neonatal deaths disproportionately falls on low- and middle-income countries where modern obstetric tools are not available to date pregnancies and monitor fetal growth accurately. The INTERGROWTH-21st gestational dating, fetal growth monitoring, and newborn size at birth standards make this possible.

Objective: To scale up the INTERGROWTH-21st standards, it is essential to assess the feasibility and acceptability of their implementation and their effect on clinical decision-making in a low-resource clinical setting.

Methods: This study protocol describes a pre-post, quasi-experimental implementation study of the standards at Jacaranda Health, a maternity hospital in peri-urban Nairobi, Kenya. All women with viable fetuses receiving antenatal and delivery services, their resulting newborns, and the clinicians caring for them from March 2016 to March 2018 are included. The study comprises a 12-month preimplementation phase, a 12-month implementation phase, and a 5-month post-implementation phase to be completed in August 2018. Quantitative clinical and qualitative data collected during the preimplementation and implementation phases will be assessed. A clinician survey was administered eight months into the implementation phase, month 20 of the study. Implementation outcomes include quantitative and qualitative analyses of feasibility, acceptability, adoption, appropriateness, fidelity, and penetration of the standards. Clinical outcomes include appropriateness of referral and effect of the standards on clinical care and decision-making. Descriptive analyses will be conducted, and comparisons will be made between pre- and postimplementation outcomes. Qualitative data will be analyzed using thematic coding and compared across time. The study was approved by the Amref Ethics and Scientific Review Committee (Kenya) and the Harvard University Institutional Review Board. Study results will be shared with stakeholders through conferences, seminars, publications, and knowledge management platforms.

Results: From October 2016 to February 2017, over 90% of all full-time Jacaranda clinicians (26/28) received at least one of the three aspects of the INTERGROWTH-21st training: gestational dating ultrasound, fetal growth monitoring ultrasound, and neonatal anthropometry standards. Following the training, implementation and evaluation of the standards in Jacaranda Health's clinical workflow will take place from March 2017 through March 5, 2018. Data analysis will be finalized, and results will be shared by August 2018.

Conclusions: The findings of this study will have major implications on the national and global scale up of the INTERGROWTH-21st standards and on the process of scaling up global standards in general, particularly in limited-resource settings.

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KEYWORDS

ultrasound; gestational age; fetal growth; health care quality; anthropometry

Introduction

Background

The neonatal period (first 28 days of life) is the most vulnerable time for an infant's survival. In 2016, 2.6 million neonates died globally representing 46% of all under-five deaths [1]. Most of these deaths took place in low- and middle-income countries (LMICs), including 80% in sub-Saharan Africa and South Asia [1]. Preterm birth related complications are the primary cause of neonatal deaths [1]. A common condition associated with preterm birth is low birth weight (LBW; <2.5 kg), which contributes to 60-80% of neonatal deaths [2] and can lead to long-term complications, including developmental delays [2-7]. There are two causes of LBW in neonates: prematurity, growth restriction during pregnancy resulting in a birthweight that is small for gestational age (SGA) [8], or a combination of the two conditions. SGA newborns have nearly twice the risk of neonatal and post-neonatal mortality [3] and account for 21.9% of neonatal deaths in LMICs [9].

To make sound clinical decisions and provide quality maternal and neonatal care, clinicians require measurement standards for accurate pregnancy dating, monitoring of fetal growth, and assessment of newborn size and growth [8]. Such standards enable clinicians to provide appropriately-timed antenatal care (ANC) [10]; identify the need for high-risk ANC consultations and referrals; and anticipate, identify, and manage fetal growth restriction [10,11], preterm labor [12,13], and maternal and neonatal [12] complications effectively [14]. The ability to date a pregnancy accurately affects a clinician's ability to make informed decisions about appropriate timing of labor induction for maternal and fetal indications (including prolonged gestation) and elective or repeat caesarean sections [15]. Accurate gestational dating is also essential for birth preparedness, allowing women to plan for transportation to a birth facility at the appropriate time [16]. Lastly, at the time of birth, correctly assessing the neonate's size for gestational age is critical for appropriate clinical management and potential referral for abnormal size and growth [17].

The date of the maternal last menstrual period (LMP) can be used for pregnancy dating but is often inaccurate or unknown; in these cases, ultrasound is the most accurate method for determining gestational age [12,18-20]. Ultrasound is also the

gold standard for monitoring fetal growth disturbances [21]. However, ultrasound equipment is not always available and fully functional in low-resource settings; even when it is, there is often a lack of trained personnel with the technical knowledge to use it effectively [22,23]. As a result, gestational age is often not determined, which makes monitoring and intervention for poor fetal growth impossible [22,23]. Because of this, the standard for assessing gestational age and fetal growth in most LMICs is date of LMP [12] and fundal height [24], respectively. The literature has shown that both methods have a high margin of error, which can lead to inaccurate dating, diagnoses, and clinical management [25-27].

In 2014, the INTERGROWTH-21st Project completed a five-year, global, prospective study of growth, health, nutrition, and neurodevelopment. The study followed women and their infants longitudinally from less than 14 weeks gestation until two years postnatal. The project enrolled populations at low risk of adverse outcome in Brazil, Italy, Oman, UK, USA, China, India, and Kenya [28,29]. INTERGROWTH-21st data were compiled to develop new prospective standards to be used to assess pregnancy dating in the first trimester [30] and second trimester [19], fetal growth [11] (including fundal height [24] and ultrasound assessment [11]), and newborn size at birth [13,17]. With these evidence- and globally-based standards, for the first time, clinicians will be able to monitor growth based on how healthy babies in any population should grow [14]. These standards complement the World Health Organization (WHO) Child Growth Standards, together offering a standardized method to assess growth throughout the continuum of fetal life through early childhood development, which is useful for both clinicians and patients.

To scale these standards and affect preterm birth and its complications, including neonatal mortality, it is essential to assess the feasibility and acceptability of implementing these standards and their effect on clinical decision-making, particularly in low-resource clinical settings.

Aim

We aim to assess the feasibility and acceptability of implementing the INTERGROWTH-21st standards over a one-year period at Jacaranda Health, a private, social enterprise maternity hospital in peri-urban Nairobi, Kenya. To our

knowledge, this is the first facility-based implementation study of the INTERGROWTH-21st standards in a limited-resource setting. The research design considers stakeholder inputs, the physical and institutional environment, and the health system structure.

The ultimate aim of the project is to use the results of the study to inform the implementation and scale up of the INTERGROWTH-21st standards in other settings and to inform the translation of guidelines and tools into routine clinical practice.

Primary Objective

The primary objective is to determine the facilitators and barriers to implementing the INTERGROWTH-21st standards at Jacaranda Health. The specific components of the primary objective are to assess the introduction of the INTERGROWTH-21st standards and the training of clinicians at Jacaranda Health, the effect of the implementation of the INTERGROWTH-21st standards on clinical practices at Jacaranda Health, clinicians' experiences and satisfaction with the INTERGROWTH-21st standards, clinicians' perceived effect of the standards on the clinical care they provide, and patient experiences and satisfaction with the care they received at Jacaranda Health during implementation of the INTERGROWTH-21st standards.

Secondary Objective

The secondary objective of this study is to assess the effect of implementing the INTERGROWTH-21st standards on clinicians' decision-making and patient outcomes, including the processes for determining gestational age and estimated due date, internal referral to Jacaranda Health clinicians providing high-risk consultations, tertiary-center referral of high-risk pregnant women, and indications for and rates of labor inductions and caesarean sections.

Methods

Study Design

This is a pre-post, quasi-experimental implementation study using quantitative clinical data, focus group discussions (FGDs), in-depth interviews (IDIs), and a short clinician survey. The study describes the feasibility, acceptability, and the effect of implementing the INTERGROWTH-21st standards on clinical decision-making and management at Jacaranda Health. Study activities consisted of a 12-month preimplementation phase which included a baseline facility assessment, changes to facility protocols and charting forms, planning work flow adaptations to facilitate implementation of the standards, equipment procurement, training of clinicians, and baseline data collection; a 12-month implementation phase which included the implementation of the INTERGROWTH-21st clinical standards, revised facility protocols and charting forms into routine clinical practice, and data collection; and a five-month post-implementation phase which includes analysis and dissemination.

This study design was based on a conceptual model created by INTERGROWTH-21st researchers at Oxford University and researchers at the Harvard T.H. Chan School of Public Health.

Study Setting

This implementation study is currently being carried out at Jacaranda Health, a social enterprise, 18-bed maternity hospital that provides women in peri-urban Nairobi with affordable, safe, and respectful ANC, standard vaginal and cesarean delivery, and postnatal care (PNC) services. Women in preterm labor and newborns with LBW and/or complications are not managed at this facility and are referred to tertiary-level facilities for specialized care. With a model that emphasizes quality and affordable care provided primarily by nurse-midwives (and supported by a team of highly skilled physicians, clinical educators, and managers), Jacaranda Health provides an ideal venue for evaluating the implementation of the INTERGROWTH-21st standards and capturing factors that facilitate and challenge that process. Jacaranda Health patients come from densely-populated, peri-urban neighborhoods in northeastern Nairobi, including Kiambu, Thika, Gatundu, and Embakasi districts. These areas are served by many facilities that range from small pharmacies and outpatient care clinics to private and public sector secondary and tertiary hospitals with maternity wards; the services and prices vary substantially across these facilities.

Study Population

Pregnant women with a viable fetus presenting for ANC and/or delivery at Jacaranda Health were eligible for the following three elements of the intervention: (1) gestational dating standards for women who present for their initial ANC visit in the first or second trimester (more than eight and less than or equal to 26 weeks gestation); (2) fetal growth monitoring standards for women who present for an ANC visit in the third trimester (after 26 weeks gestation) and are identified as high-risk based on factors related to their surgical, medical, or obstetric history or current pregnancy; and (3) newborn size at birth standards for all newborns born at Jacaranda Health. We excluded pregnant women with a nonviable fetus in both quantitative and qualitative data collection, women who present for their initial ANC visit in the third trimester (after 26 weeks gestation) for gestational dating standards, and parents of stillborn infants in qualitative data collection. All eligible pregnant women and mothers of newborns described above were eligible to participate in FGDs and IDIs.

All clinicians delivering ANC and newborn anthropometry who attended INTERGROWTH-21st training sessions are eligible to participate in FGDs, IDIs, and a short clinician survey. Clinicians who only work in child wellness clinics and not in prenatal or intrapartum care units were excluded.

Patient and Public Involvement

The development of the study design, research questions, and outcome measures did not formally involve patient and public opinions and contributions. However, the study assesses patient and provider perceptions and experiences of the implementation of the INTERGROWTH-21st standards at Jacaranda Health to

assess their acceptability and inform their further scale up. The results of the study will be disseminated to providers at Jacaranda Health by study staff at the end of the study.

Preimplementation Phase

Baseline Facility Assessment

Before implementing the INTERGROWTH-21st standards, we conducted a baseline assessment of current facility practices as they relate to our study objectives. Focus was placed on policies and practices related to ANC provision, pregnancy dating, identification and referral of high-risk pregnancies to high-risk care within Jacaranda Health and to tertiary facilities, fetal growth monitoring, newborn size measurement, and indications for and rates of cesarean section and labor induction.

The baseline assessment was conducted through clinic observations; a desk review of written policies; IDIs with Jacaranda Health's director of clinical operations, clinical programs manager, and clinical educator; a chart review to understand clinician practices and indications for and rates of cesarean sections and labor inductions; an equipment and supply inventory with a focus on ultrasound and newborn anthropometry; and a human resource inventory to understand existing personnel and clinician roles and responsibilities related to clinic flow, pregnancy dating, fetal growth monitoring, and patient counseling. We then adapted ANC protocols to align with the 2002 WHO ANC model [31]. This work was done prior to the release of the 2016 WHO ANC recommendations [32].

Protocol, Charting, Equipment, and Work Flow Adaptations

A key element of preimplementation activities was ensuring that the hospital's equipment, protocols, and procedures were updated and adapted for the implementation of the INTERGROWTH-21st standards. In partnership with Oxford University, we created a computerized calculator to calculate gestational age and fetal growth percentiles: clinicians use the ultrasound machine to measure the required biometrics for gestational dating or fetal growth, input the measurements into the calculator, and then record the resulting gestational age or fetal growth percentiles in the patient's chart. Additionally, neonatal scales, measuring tapes, and infantometers, chosen in consultation with the INTERGROWTH-21st Oxford team and adjusted based on local availability and resource constraints, were sourced and integrated into clinical practice.

We updated Jacaranda Health clinical protocols for standard ANC, high-risk pregnancy classification and subsequent internal and tertiary-center referral, gestational dating, fetal growth monitoring, and newborn anthropometry, in addition to corresponding patient charting forms, to support the implementation and evaluation of the INTERGROWTH-21st standards.

Clinician job aids were created to facilitate the implementation of the standards and related decision-making algorithms. We also altered clinic flow processes to accommodate the introduction of ultrasound services; a separate room was

designated exclusively for gestational dating ultrasounds. In the context of adapting clinical definitions of high-risk pregnancy criteria and processes for both internal and tertiary-center referrals, we trained clinicians to only do activities (like ultrasound) within their scope of practice as determined by the Nursing Council of Kenya.

Training

A main aim of implementation was training Jacaranda Health staff how to use the INTERGROWTH-21st standards. This was done in collaboration with the original INTERGROWTH-21st Project study team based at Oxford University and Aga Khan University Hospital (AKUH) in Nairobi, Kenya [33-37].

From October 2016 to February 2017, we conducted training of Jacaranda Health clinical and management staff on the purpose and use of the INTERGROWTH-21st gestational dating ultrasound, fetal growth monitoring ultrasound, and neonatal anthropometry standards. Emphasis was placed on including assessment, identification, and referral of high-risk patients as part of the study design to evaluate operational system capacity to support the implementation of the standards and their clinical implications.

An obstetrician-led half-day training included essential components of ANC, basic obstetric ultrasound skills, and the INTERGROWTH-21st standards and accompanying adaptations to charting practices and clinical protocols. Of the 23 participants in the training, 22 were nurse-midwives and one was a clinical officer; these staff provide the majority of ANC and PNC at Jacaranda Health.

An obstetrician and an INTERGROWTH-21st anthropometry trainer from AKUH provided a half-day anthropometry training which included theory, equipment, and techniques needed to perform accurate newborn length, weight, and head circumference measurements. The anthropometry trainer certified clinicians in neonatal anthropometry after they performed length, weight, and head circumference measurements accurately on newborns. One group of 24 clinicians, 23 nurse-midwives and one clinical officer, attended this training. Nearly 90% (24/28) of all full-time and part-time Jacaranda Health clinicians attended these initial trainings.

AKUH trained Jacaranda Health's primary sonographer in INTERGROWTH-21st ultrasound measurements for the first, second, and third trimesters over the course of two weeks. At the end of the two weeks, the sonographer demonstrated proficiency in performing INTERGROWTH-21st measurements as determined by a senior radiologist at AKUH. The Jacaranda Health sonographer then trained a group of six Jacaranda Health nurse-midwives with prior experience in basic obstetric ultrasound during a half-day training on gestational dating ultrasounds. Three of the six nurse-midwives were certified to perform gestational dating ultrasounds after proving competence in performing measurements and calculating estimated delivery date accurately three consecutive times in the presence of the sonographer. This group of three nurse-midwives constitutes over 10% (3/28) of all clinicians.

Implementation Phase

After training was completed and equipment was put into place, the INTERGROWTH-21st standards, revised facility protocols, and adapted patient charting forms were introduced into routine clinical practice in March 2017. The clinic work flow adaptations were implemented to facilitate the identification of pregnant women eligible for ultrasound using the new standards and ensure that pregnant women were seen by the appropriate clinician. Work flow adaptations were not needed to implement the newborn size at birth standards since newborn anthropometry was an established part of routine practice.

Quality Monitoring

To ensure the quality of the implementation of the INTERGROWTH-21st standards, three quality monitoring processes were utilized: expert ultrasound image review, weekly clinic stakeholder meetings, and targeted refresher training. Our protocol includes sending copies of de-identified gestational dating and fetal growth ultrasound images to the quality assurance team at Oxford University. The team reviews the images, assesses the quality of each image based on INTERGROWTH-21st guidelines, and provides guidance to Jacaranda Health staff on how to improve ultrasound quality, if needed. Images were sent to Oxford for review every two months via a double password-protected Dropbox folder. The program management team at Jacaranda Health then shared feedback from the Oxford team with the ultrasound providers to strengthen sonography skills and processes. Reinforcement training was provided by Oxford University clinical researchers specializing in sonography midway through implementation to further improve the quality of the ultrasound procedures. Challenges in clinical implementation were discussed by the clinical staff during weekly meetings, which enabled staff to quickly resolve any problems. Lastly, through chart review and observation, the clinical and project management teams had the discretion to identify clinicians who required targeted refresher training and to provide that training at any point during the study. Important project notifications and reminders were administered to all staff at weekly clinical meetings by clinic managers and project management.

Study outcomes

Primary outcomes

The primary study outcomes are (1) clinicians' and patients' perception of facilitators and barriers to the implementation of the INTERGROWTH-21st standards and (2) uptake of gestational dating ultrasounds, fetal growth monitoring by ultrasound, and newborn anthropometry. These outcomes were explored through the following dimensions: feasibility, acceptability, appropriateness, adoption, fidelity and penetration [38].

Secondary outcomes

The secondary outcomes used to evaluate clinical decision-making include (1) proportion of ANC clients whose gestational age and estimated due date were correctly calculated and documented, (2) proportion of high-risk pregnant women who were referred internally to a high-risk clinician or to a tertiary care facility, (3) proportion of pregnant women receiving gestational dating scans who were induced for labor due to a prolonged pregnancy, and (4) proportion of pregnant women receiving gestational dating scans who delivered via cesarean section.

Data collection

During the preimplementation phase, baseline data were collected for 12 consecutive months (months 1-12) prior to the start of the implementation phase. Data were also collected for 12 consecutive months during the implementation phase (months 13-24). These preimplementation and implementation phase quantitative data come from patient charting forms completed in the two-year period. Qualitative data were also collected during the preimplementation phase (month eight) and the implementation phase (month 16 and month 24). Additionally, a one-time short provider survey was administered during the implementation phase at month 20 to assess clinicians' attitudes and acceptability of the standards. (Table 1).

Quantitative Data Collection

We collected outcome data from patient charts and from a clinic log of external referrals for pregnancies and deliveries one year before and one year after the start of implementation.

Table 1. Data collection tools and timeline.

Method and tool	Preimplementation (months 1-12)		Implementation (months 13-24)			
	Month 8	Months 1-12	Month 16	Month 20	Month 24	Months 13-24
Quantitative						
Chart review		X				X
Clinic referral log		X				X
Qualitative						
Patient in-depth interviews	X		X		X	
Patient focus group discussions	X		X		X	
Clinician in-depth interviews	X		X		X	
Clinician focus group discussions	X		X		X	
Clinician survey				X		

Qualitative Data Collection

We conducted FGDs and IDIs with participants sampled from two population groups using purposeful and convenience sampling: (1) patients who received ANC and/or delivery care at Jacaranda Health and (2) clinicians who work directly with patients (providing ANC, delivery care, or anthropometry at birth) including nurse-midwives, hospital managers, ultrasonographers, and physicians.

FGDs and IDIs with patients and clinicians were conducted in the preimplementation phase and twice during the implementation phase. Patients were interviewed to evaluate their perceptions, attitudes, and experiences of receiving an ultrasound for gestational dating and fetal growth, their newborn receiving a growth assessment, and their interactions with clinicians implementing this care. Clinicians were interviewed to evaluate their perceptions, attitudes, and experiences of the introduction and implementation of the new standards as part of their routine clinical practice.

The research team developed semistructured discussion guides for both FGDs and IDIs, which were piloted with Jacaranda Health staff and patients. Research assistants conducted all interviews in a private and secure location and took great care to protect the identity and confidentiality of all participants. To encourage patient participation in qualitative interviews, we offered reimbursement for transportation to the facility and free refreshments after the completion of the interviews. All FGDs and IDIs were audio-recorded and transcribed verbatim by an external transcriber; in the instances that participants spoke a language other than English, the transcriber translated the recording to English for the transcript. Hand-written notes taken by the research assistant provided the context for the interviews.

Additionally, a survey (10 questions) was administered by a research assistant to all clinicians during the implementation phase at month 20 via Survey Monkey on an Android tablet. Clinicians were asked to grade their comfort (using a Likert scale) with the INTERGROWTH-21st standards, the ease of integration into their workflow, and their perceptions of the effect of the standards on the quality of care they provided.

Sample Size

We used a census of clinicians and patients for this implementation study based on the inclusion and exclusion criteria described prior. According to clinic estimates and projections of ANC and delivery care utilization, data for up to 5,000 pregnant women and newborns will be recorded. The total number included in the final analysis will be based on the number of patients who meet eligibility criteria as confirmed at the time of data entry based on indicators in patient charting forms.

In each time period, the sample will be stratified into the following three categories: (1) pregnant women who attended ANC at Jacaranda Health and delivered there, allowing analysis of longitudinal ANC and delivery data; (2) pregnant women who attended ANC at Jacaranda Health but did not deliver there, providing ANC data only; and (3) women who did not attend ANC but who delivered at Jacaranda Health, capturing delivery and newborn data only. All clinic managers, physicians, and

nurse-midwives who met the criteria are included. Clinician attrition will be documented.

Postimplementation Phase

Data Analysis and Management

Quantitative Data

Data from patient charts and referral logs were double-entered and managed in REDCap [39], a secure online data capture system with built-in data entry restrictions, data quality tools, and protection of personally identifiable information. Quality control measures have been in place to check the data at various stages on a routine basis using REDCap [39] and Stata 15 [40]. REDCap's data quality features were utilized to ensure that data was entered within acceptable ranges and in the proper formats [39]. Additionally, data were checked for consistency and errors using a Stata 15 [40] script. All discrepancies have been resolved by checking original paper charts.

Most implementation and process indicators will be measured and presented using descriptive statistics. We will analyze changes in quantitative outcomes where relevant, by evaluating the difference in response to the indicators between pre- and postimplementation. Measurements of differences in continuous data will be assessed using t-tests for data that is normally distributed; otherwise, a non-parametric test will be performed. Categorical data will be compared using a chi-squared test. Quantitative data will be analyzed using Stata 15 [40]. All data will be de-identified before analysis begins.

Qualitative Data

For each cycle of qualitative data transcription, the transcriber completed transcription of one initial data file and sent it to the qualitative data manager at Jacaranda Health for quality control prior to transcribing the rest of the data files.

Qualitative data collected at each stage are being analyzed independently by two investigators using thematic coding in NVivo [41] and compared across time. Transcribed, de-identified qualitative data are being stored in a double password-protected Dropbox folder accessible only to a select number of study personnel.

Dissemination Policy

Results of the study will be shared with key stakeholders both in Kenya and globally through a national dissemination meeting, global conferences, an online knowledge management platform, and publications.

Ethical Considerations

The Amref Ethics and Scientific Review Committee of Kenya and the Harvard University Institutional Review Board approved all study activities, protocols, and standards prior to the commencement of study activities.

Facility-level informed consent was obtained from the Jacaranda Health hospital manager, acting as the facility's representative, prior to the collection of any implementation data. The facility informed consent emphasized that no patient-identifiable health data would be shared or disseminated beyond the Jacaranda Health team. All FGD, IDI, and survey participants—patients

and clinicians—provided written informed consent prior to any interview. Participants were informed that they could withdraw their consent at any time and be removed from the sample.

Results

From October 2016 to February 2017, over 90% of all Jacaranda Health clinicians (25 nurse-midwives and one clinical officer of 28 total Jacaranda Health clinicians) received at least one of the three aspects of the INTERGROWTH-21st training: gestational dating ultrasound, fetal growth monitoring ultrasound, and neonatal anthropometry standards. Following the training, the implementation and study of the INTERGROWTH-21st standards as part of Jacaranda's clinical workflow took place from March 2017 through March 5, 2018. Data analysis will be finalized, and results are expected in August 2018.

Discussion

Significance

The findings of this study will have major implications on the national and global scale up of the INTERGROWTH-21st standards and on the process of scaling up global standards in general, particularly in limited-resource settings. The ability to implement a standard methodology of gestational dating, fetal growth monitoring, and assessment of newborn size at birth will result in better data to enable clinicians, researchers, and policy makers to more accurately identify and quantify high-risk pregnancies, preterm birth, and fetal and neonatal growth disturbances. In turn, standardized data that is comparable across global populations empowers researchers and policy makers to better understand and act on distributions of high-risk pregnancies, restricted growth, and prematurity. Lastly, based on this data, clinical practice and resources can be modified to

meet the needs of pregnant women and their fetuses and newborns to decrease the incidence and morbidities associated with poor fetal and newborn growth and prematurity.

Limitations

While Jacaranda Health provides the right environment for this study, the generalizability of our findings needs to be carefully considered when applying lessons learned to other clinical settings. Given that clinic protocols were amended to meet the 2002 WHO ANC guidelines, which affected the criteria for high-risk referral, this change may confound the outcome of the percentage of women who are referred to high-risk care. The study is also limited in its ability to assess the long-term health outcomes of these standards, yet it will inform future research designed to assess them.

Strengths

This will be the first study to assess the feasibility and acceptability of introducing the new INTERGROWTH-21st clinical standards into a low-resource setting. Due to the dearth of innovative gestational dating tools and burden of preterm birth in low-resource settings, it is particularly important to study the implementation of these standards in this setting. The results of our evaluation will provide useful insights and recommendations for further implementation in similar clinical settings in Kenya and beyond.

Additionally, the mixed-methods approach used in this study will yield unique insights into the barriers, facilitators, and process of implementing the INTERGROWTH-21st standards and the resulting impact on short-term clinical decision-making. Lastly, Jacaranda Health is dedicated to health facility quality improvement in peri-urban Nairobi, which makes it an excellent venue for evaluating the implementation of the INTERGROWTH-21st standards and for capturing factors that facilitate and challenge that process.

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Authors' Contributions

All authors contributed to the development of the design of the implementation study. All authors also reviewed and approved the final manuscript. KM, MM, SP, LV, and SS drafted the protocol and manuscript with regular input from AL, JV, MNW and ATP and occasional feedback from CO, FM, RMJ, SL and NP. The study was conceptualized by KM, LV, AL, JV, ATP, and SP. KM, LV, MM, RMJ, SL and SS provided project management and coordination of the study. KM, SP, SS, MM, LV, ATP, and CO created the protocols and training materials for the study. KM, LV, SS, RMJ, SP, and MM designed the data collection instruments. LV and MM designed the database and data management systems. LV, KM, MM, RMJ, and SS created the data analysis plan for the study.

Conflicts of Interest

All authors have completed the ICMJE uniform disclosure form and declare ATP is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) and all other authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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Abbreviations

AKUH: Aga Khan University Hospital
ANC: antenatal care
FGD: focus group discussion
IDI: in-depth interview
LBW: low birth weight
LMICs: low- and middle-income countries
LMP: last menstrual period
PNC: postnatal care
SGA: small for gestational age
WHO: World Health Organization

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Protocol

Prospective Epidemiological Research on Functioning Outcomes Related to Major Depressive Disorder in Japan (PERFORM-J): Protocol for a Prospective Cohort Study

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Abstract

Background: Patients with major depressive disorder may exhibit cognitive dysfunction that can affect functional outcomes. However, the prevalence and burden of cognitive dysfunction in Japanese patients with MDD have not been thoroughly examined.

Objective: To investigate the time course (over 6 months) of several functional outcomes during treatment with antidepressants in Japanese patients with major depressive disorder. The primary objective is to assess longitudinal changes in cognitive function and depressive symptoms, using both clinician-rated and patient-rated scales. The study incorporates assessments of cognitive function and other functional outcomes (functional capacity, disability, work productivity and impairments of activity, and quality of life), as well as depressive symptoms.

Methods: PERFORM-J (Prospective Epidemiological Research on Functioning Outcomes Related to Major Depressive Disorder in Japan) is a 6-month, prospective, multi-center, epidemiological cohort study. Participants are Japanese outpatients aged 18-65 years with a recurrent or new diagnosis of a major depressive episode (according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR]), who are initiating a new antidepressant as monotherapy (either as first-line therapy or after switching from a previous antidepressant). Eligible patients are evaluated objectively during four visits (at baseline and at Months 1, 2, and 6) using physician-rated assessments of severity of depressive symptoms, cognitive function, and functional capacity. Subjective, patient-reported, outcomes are also assessed as indicators of depressive symptoms, disability, work productivity or impairments of activity, and perceived cognitive dysfunction.

Results: The study began in September 2016. Patient enrollment was completed on June 30, 2017, with 523 patients having been enrolled from 48 study sites. As of October, 2017, 279 patients had completed the study.

Conclusions: PERFORM-J is expected to provide valuable information on the longitudinal relationship between cognitive dysfunction, depressive symptoms, and other functional outcomes in Japanese patients with major depressive disorder who initiate monotherapy with antidepressants.

Trial Registration: UMIN Clinical Trials Registry UMIN000024320; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000028011 (Archived by WebCite at <http://www.webcitation.org/70K7W9PgC>).

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KEYWORDS

antidepressants; depression; major depressive disorder; cognitive dysfunction; observational study

Introduction

Major depressive disorder (MDD) is a common psychiatric condition, with an estimated 12-month prevalence of 2.2% in Japan [1,2]. Although mood disturbances are characteristic of patients with MDD, there is accumulating evidence for the presence of cognitive dysfunction, linked with poor functional outcomes [3-5]. For example, in a recent large-scale, cross-sectional study conducted in six Asian countries and territories, 67% of currently depressed, nonmedicated outpatients reported subjective memory deficits and 73% experienced concentration deficits [6]. In addition, Japanese treatment guidelines for depression recommend that cognitive function should be carefully monitored, even after remission of depressive (affective) symptoms has been achieved [7]. This is partly due to a possibility of relapse of affective symptoms (attributable to the continued presence of cognitive dysfunction) once patients return to normal daily activities. Little is known, however, about longitudinal changes in cognitive function throughout depressive episodes and periods of remission, or the impact of cognitive dysfunction on symptomatic remission and functional recovery in patients with MDD.

PERFORM (Prospective Epidemiological Research on Functioning Outcomes Related to Major Depressive Disorder; NCT01427439) was a 2-year, prospective, noninterventional cohort study of European patients with MDD, conducted in real-world settings in France, the UK, Spain, Germany, and Sweden [8,9]. The study aimed to investigate changes in cognitive function and functional outcomes during depressive episodes. The findings suggest that perceived cognitive dysfunction is linked with poor overall functioning, including reductions in work productivity and impairment in quality of life. Moreover, the relationships between cognition and functional outcomes were not fully explained by changes in severity of depressive symptoms [8]. Additionally, depressive symptoms and disturbances in self-perceived cognition followed different trajectories during treatment with antidepressants; improvements in cognitive function were more gradual than improvements in mood symptoms, with a lesser magnitude [8].

The same investigators reported a significant association between residual subjective cognitive deficit (assessed using the five-item Perceived Deficit Questionnaire [PDQ-5] [10]) and subsequent relapse (assessed 6 months later) in MDD patients whose symptoms had remitted during treatment for 2 months [9]. In fact, the odds of relapse increased by 12% with each unit increase in PDQ-5 score. Based on these observations, the authors concluded that residual mood symptoms may identify patients at risk of relapse, and that interventions to reduce residual cognitive dysfunction may potentially reduce

the risk of relapse of depressive symptoms [9]. Due to regulations around noninterventional studies in Europe, PERFORM employed patient-rated scales but limited application of physician-rated measures. However, reports by patients do not always correlate well with physician-rated outcomes [11,12].

Results from the World Mental Health Japan Survey suggest that the male to female ratios in both prevalence and persistence of depression in Japan are different from those reported in Western countries: prevalence is higher in middle-aged men, while persistence is higher among women and younger groups [1]. Furthermore, treatment rates in Japan are lower than those in high-income Western countries, which may be partially explained by less health service expenditure, [13] and partially by the stigma associated with mental illnesses in Japan [1]. Such differences suggest that the findings of the PERFORM study may not be extrapolated to Japanese patients and warrant further investigation. To our knowledge, no studies have explored longitudinal changes in cognitive function and higher-level functional outcomes during treatment of Japanese patients with MDD [14]. To increase awareness of cognitive dysfunction in depression in Japan, we have designed a prospective observational study (PERFORM-J; UMIN Clinical Trials Registry: UMIN000024320), based on the original PERFORM study. Since patient-rated and physician-rated measures seem to represent qualitatively different aspects of cognition and psychosocial function, both tools are used in PERFORM-J to explore longitudinal changes in cognitive function and other aspects of functional outcomes in Japanese patients with MDD.

Methods

Study Objectives

The primary objective of PERFORM-J is to examine longitudinal changes in cognitive function and depressive symptoms in patients with MDD over a period of 6 months, following the start of treatment with an antidepressant in routine clinical practice. Secondary objectives are (1) to determine the number of patients with cognitive dysfunction and/or depressive symptoms across the study period; (2) to examine the relationship between cognitive disturbance and psychosocial function and work productivity or activity impairment; and (3) to compare quality of life and utilization of healthcare resources longitudinally, between patients with different severities of cognitive dysfunction. Additional exploratory objectives are (1) to determine whether the presence of cognitive dysfunction is a risk factor for treatment refractory depressive symptoms at month 1, failure to achieve symptomatic remission at month 2 or 6, and relapse of depressive symptoms at month 6; and (2)

to investigate the association between cognitive dysfunction and functional capacity.

Patients

Eligible participants are Japanese outpatients aged 18-65 years with a recurrent or new diagnosis of a major depressive episode (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-IV-TR]), who initiate a new antidepressant as monotherapy (a tricyclic or tetracyclic antidepressant, selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor, or noradrenergic and/or serotonergic antidepressant) either as first-line therapy or switching from a previous antidepressant, based on the judgement of their physician. The baseline visit is defined as a clinic visit at which the new antidepressant is initiated. The full eligibility criteria are shown in [Textbox 1](#). Eligible patients are enrolled during the first visit (visit 1). As the study is conducted

during routine clinical practice, following enrollment (on initiation of a new antidepressant as monotherapy) subsequent addition of other antidepressants (and subsequent dose modification) is permitted during the study period, and use of other concomitant medications is permitted. The dosage and administration of antidepressants are in accordance with general prescribing instructions.

Assessments

During the baseline visit, informed consent is obtained, and eligibility to participate in the study is determined (according to the criteria in [Textbox 1](#)). Demographic data are then collected, before the new antidepressant is prescribed, as detailed in [Table 1](#). Information on the management of MDD and utilization of healthcare resources is also collected at each subsequent visit.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria
1. An outpatient.
2. Aged between 18 and 65 years at the time of giving informed consent.
3. With a recurrent or new diagnosis of a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV-TR); the diagnosis is confirmed using the Major Depressive Episode module of the Mini International Psychiatric Interview (MINI) [15].
4. Initiating a new antidepressant as monotherapy (a tricyclic or tetracyclic antidepressant, a selective serotonin reuptake inhibitor, a serotonin–norepinephrine reuptake inhibitor, or a noradrenergic and specific serotonergic antidepressant) at the baseline visit (either as first-line therapy or after switching from a previous antidepressant), as decided by the investigator.
5. Capable of understanding the content of the clinical research and complying with the research protocol requirements (in the opinion of the investigator)
6. Capable of signing and dating an informed consent form, before initiation of the clinical research procedures.
7. Capable of reading and understanding the research questionnaires.
Exclusion criteria
1. A concurrent diagnosis or history of any of the following conditions: <ul style="list-style-type: none"> • schizophrenia or other psychotic disorders • bipolar disorder • dementia, or any other neurodegenerative disease • substance dependence, including dependence on alcohol and other drugs, but not including mild and moderate nicotine dependence; patients with severe nicotine dependence are excluded • any psychiatric disorder due to a general medical condition or substance misuse.
2. A prescription for more than one antidepressant on the day of the baseline visit (for example, a combination of two or more antidepressants).
3. An antipsychotic prescription on the day of the baseline visit.
4. A prescription for a mood stabilizer on the day of the baseline visit.
5. Current treatment with electroconvulsive therapy or repeated transcranial magnetic stimulation.
6. Pregnant or breastfeeding (female patients) at the beginning of the study.
7. Acute suicidality (in the opinion of the investigator).
8. Currently enrolled in an interventional clinical research study, such as a clinical trial.
9. A workmate of the investigator or his/her immediate family, or a subordinate of the investigator or their immediate family.
10. Prior enrolment in the study.
11. Unlikely to comply with the protocol (in the opinion of the investigator).

Table 1. Data collection (DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-IV; MDD: Major Depressive Disorder; VAS: visual-analogue scores).

Data to be collected	Details
Demographic information	Age; gender; weight; height; use of tobacco; marital status; living area; educational level; employment status
MDD history	Number of depressive episodes; timing and treatment of previous depressive episode; history of suicide attempts and hospitalizations for depression; concomitant mental and somatic conditions (including diagnosis and treatment, if relevant)
Management of current episode of MDD	Antidepressant treatments prescribed; concomitant psychotropic treatments; use of psychotherapy
Utilization of healthcare resources	Number of visits to physicians or other health care professionals; hospitalizations (duration; ward; relationship to depression) and absences from employment due to illness (duration and relationship to depression) due to any problems (not limited to MDD symptoms)
Life events	Occurrence of critical life events (eg, death of a family member/relative; unemployment, relocation)
Physician-rated assessments	
Mini International Neuropsychiatric Interview (MINI) [15]	Brief structured diagnostic interview for major Axis I psychiatric disorders in DSM-IV-TR. Diagnosis of major depressive episode confirmed using "Major Depressive Episode" module
Clinical Global Impression - Severity (CGI-S) scale [17]	Patient's current state of mental illness, according to the physician's experience. 7-point scale from 1 (normal; not at all ill); to 7 (among the most extremely ill patients)
Montgomery-Asberg Depression Rating Scale (MADRS) [18]	Severity of depressive episodes. 10 items rated from 0 (normal findings or absence of symptoms) to 6 (severe depressive symptoms). Total score=0–60 (higher score=more severe depression). Remission indicated by score ≤10
Digit Symbol Substitution Test (DSST) [16,25]	Speed of psychomotor performance (visual perception, spatial decision-making, and motor skills). The task is to match 133 digits with simple symbols in 120 seconds. Correct answers are counted; score=0–133
University of California, San Diego, Performance-based Skills Assessment-Brief (UPSA-B) ^a [19,26]	Functional skills in patients with mental illness (brief version of the role-play-based performance test battery). Two subscales (managing finances and communication with others); raw scores are rescaled to a range of 0 to 100. Higher score=greater functional capability
Patient-reported outcomes	
Patient Health Questionnaire-9 item (PHQ-9) [20,27]	Depressive symptoms. 9 items rated from 0 (not all) to 3 (nearly every day). Total score=0 (absence of depression) to 27 (severe depression)
Sheehan Disability Scale (SDS) [21]	Disability assessed in three domains (work/school; social life/leisure activities; family life/home duties). Three discretized 10-point VAS from 0 (no disability) to 10 (extreme disability). The sum of scores provides a single measure of global functional impairment: range=0 (unimpaired) to 30 (highly impaired)
Work Productivity and Activity Impairment (WPAI) questionnaire [22]	Work productivity/impairment in activity in past 7 days (6 items). Yields scores for: absenteeism; presenteeism; loss of work productivity; and impairment of activity. Outcomes are expressed as % impairment. Higher scores=worse outcomes
Perceived Deficits Questionnaire-Depression (PDQ-D) [23]	Perceived cognitive deficits in MDD patients. 20 items in 4 subscales: attention/concentration; retrospective memory; prospective memory; planning/organisation. Score=0 (never in past 7 days) to 4 (very often, more than once a day). Total score=sum of raw scores; range=0 to 80. High score=poorly perceived cognitive dysfunction
EuroQol 5-Dimensions, 5-Levels Questionnaire (EQ-5D-5L) [24]	Generic health status (preference-based measure of well-being). Five items: mobility, self-care, usual activities, pain/discomfort, depression/anxiety, plus VAS for overall health state. Used to calculate a utility index: range=0 (death) to 1 (perfect health). VAS scores range from 0 (worst health state) to 100 (best health state)

^aTo be performed only in patients from preselected research sites (approximately 100 patients).

At the beginning of the study (baseline; visit 1), month 1 (visit 2), month 2 (visit 3), and month 6 (visit 4), severity of the illness, depressive symptoms, and cognitive function are assessed using the Clinical Global Impressions-Severity (CGI-S) scale, the Montgomery-Asberg Depression Rating Scale (MADRS), and the Digit Symbol Substitution Test (DSST), respectively [16-18]. Functional capacity is evaluated for a

subset of approximately 100 patients at selected sites using the University of California, San Diego Performance-based Skills Assessment-Brief (UPSA-B) [19]. Additionally, all patients are asked to complete the following self-assessment questionnaires to evaluate subjective depressive symptoms, cognition, social function, and quality of life: the Patient Health Questionnaire-9 item (PHQ-9) [20]; Sheehan Disability Scale (SDS) [21]; Work

Productivity and Activity Impairment questionnaire (WPAI) [22]; Perceived Deficits Questionnaire-Depression (PDQ-D) [23]; and EuroQol5-Dimension, 5-Level (EQ-5D-5L) [24]. Details of all physician-rated and self-reported assessment tools are provided in Table 1. Validated Japanese versions of these assessment tools are used [25-27]. The same instruments are administered at each visit throughout the course of the study (Table 2). The investigators will inform the marketing authorization holders of each drug if suspected adverse events occur.

The study is conducted in accordance with the ethical principles described in the Declaration of Helsinki and the Japanese Ethical Guideline for Clinical Research, as well as all other applicable laws and regulations. Ethical review committees are constituted according to the regulations and approve the study protocol at each site before commencement of the study. Patients are required to provide written informed consent and are free to withdraw from the study at any time.

Table 2. Schedule of assessments (CGI-S: Clinical Global Impression-Severity; DSST: Digit Symbol Substitution Test; EQ-5D-5L: EuroQoL 5-Dimensions, 5-levels Questionnaire; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major Depressive Disorder; MINI: Mini International Neuropsychiatric Interview; PDQ-D: Perceived Deficits Questionnaire-Depression; PHQ-9: Patient Health Questionnaire-9 item; SDS: Sheehan Disability Scale; UPSA-B: University of California, San Diego Performance-based Skills Assessment-Brief; WPAI: Work Productivity and Activity Impairment questionnaire).

Study visit	1	2	3	4
Approximate time of visit, months	Baseline	Month 1	Month 2	Month 6
Approximate time of visit, days	Day 1	Day 29	Day 57	Day 169
Allowance, days ^a	1	22 to 36	43 to 71	141 to 197
Patient information/consent	X ^b			
Demographics	X			
MDD history	X			
Occurrence of life events	X			
MDD management	X	X	X	X
Healthcare resource use	X	X	X	X
Physician-rated assessments				
CGI-S	X	X	X	X
MINI	X			
MADRS	X	X	X	X
DSST	X		X	X
UPSA-B ^c	X		X	X
Patient-reported outcomes				
PHQ-9	X	X	X	X
SDS	X	X	X	X
WPAI	X	X	X	X
PDQ-D	X	X	X	X
EQ-5D-5L	X	X	X	X

^aThe starting date of antidepressant treatment (ie, the first day of administration) is defined as Day 1.

^bInformed consent is required before any clinical research procedures are performed.

^cConducted only in patients at preselected research sites (approximately 100 patients).

Statistical Analysis

The analysis population will comprise all eligible patients who complete at least one DSST assessment during the study period. Analyses will be based on observed cases, with no imputation of missing data.

For the primary analyses, changes from baseline at each assessment time point will be calculated for DSST and MADRS scores. Individual DSST scores will be allocated to one of four categories, as follows: within norm; 0.33-0.67 SD below norm; 0.67-1 SD below norm; or ≥ 1 SD below norm. Separately, DSST scores will be allocated to dichotomous (yes/no) categories as follows: within norm; ≥ 0.33 SD below norm; ≥ 0.67 SD below norm; ≥ 1 SD below norm. All cutoff values will be adjusted for the patient's age at baseline, as described in the Wechsler Adult Intelligent Scale - Third Edition (Japanese translation) [25]. MADRS scores will be categorized as none, mild, moderate or severe, as previously described [28,29].

For the secondary analyses, changes from baseline at each assessment time point will be calculated for SDS, WPAI, UPSA-B, PDQ-D and EQ-5D-5L scores. The association between cognitive function and depressive symptoms will be assessed using the DSST and MADRS categories at each visit. Correlations between DSST scores and SDS, WPAI, and EQ-5D-5L scores (individually) will be calculated using Pearson's and Spearman's correlation coefficients. SDS, WPAI, UPSA-B, and EQ-5D-5L scores at each assessment point will be compared using analysis of variance models, according to the DSST category at baseline. Similar analysis will be performed for PDQ-D as the primary measure of cognitive function (scores will be allocated to one of four categories; the cutoffs being based on quartiles).

As an exploratory investigation, univariate and multivariate logistic regression analyses will be conducted to determine whether the presence of cognitive dysfunction is a predictor of response, remission, and relapse of depressive symptoms. Patients with a $\geq 50\%$ reduction from baseline in MADRS score at month 1 are categorized as treatment responders. Patients with a MADRS score of ≤ 10 at month 2 and/or 6 are categorized as having achieved symptomatic remission. Patients who achieved remission at an earlier visit and have a MADRS score ≥ 22 at month 6 are categorized as having relapsed in terms of depressive symptoms. Factors for the logistic regression analyses (eg, DSST score, PDQ-D score, MADRS score, age, gender, educational level, and employment status), will be selected for their clinical relevance based on the literature [9]. Exploratory analyses will also evaluate correlations between scores on the UPSA-B, DSST, WPAI (if the sample size allows), EQ-5D-5L, and MADRS scales. Statistical tests will be two-sided at the 5% significance level, if not otherwise specified.

In subgroup analyses, all data will be summarized according to the MADRS category at baseline, and according to age group.

A target sample size of 500 patients was estimated in order to ensure acceptable precision of the mean change from baseline in DSST scores at months 2 and 6. Based on two previous studies which investigated the effect of vortioxetine on cognitive function in MDD [30,31], assuming a standard deviation of 8.1 and a withdrawal rate of 25% at month 6, 500 enrolled patients will ensure a value of 0.82 for the half-width of the two-sided 95% confidence interval for the change in DSST score from baseline to month 6.

Results

The PERFORM-J study began in September 2016. Patient enrollment was completed on June 30, 2017, with 523 patients

having been enrolled from 48 sites, with the UPSA-B assessment having been conducted on 141 patients. As of October 2017, 279 patients have completed the study.

Discussion

PERFORM-J is the first study conducted in Japan to prospectively evaluate longitudinal changes in cognitive function, depressive symptoms, and other functional outcomes in patients with MDD following the start of antidepressant therapy. The information obtained will shape our understanding of how antidepressants affect cognition in Japanese patients. Importantly, the study includes both physician- and patient-rated tests of cognitive function, administered to a large group of patients treated in accordance with current clinical practice in Japan. A noninterventional design was chosen to avoid interference with standard practice.

The prospective design and the number of study sites should facilitate collection of data that is sufficient to represent the MDD population in Japan. The 6-month study period should be long enough to detect the effects of antidepressants on depressive symptoms. The study period will also allow detection of meaningful changes in functional outcomes and utilization of healthcare resources over time. In fact, the study design is similar to that of PROACT (Prospective Research Observation to Assess Cognition in Treated MDD patients), currently ongoing in China, and PERFORM-K in South Korea [32].

Currently, cognitive function does not appear to be a major concern among Japanese psychiatrists who treat mood disorders. Therefore, the current study should provide valuable information to facilitate improvements in functional outcomes in patients with MDD.

A major limitation of this study relates to the uncontrolled and observational study design, which does not allow evaluation of cause and effect relationships. Additionally, patients can take concomitant medication, potential effects of which on cognition cannot be excluded.

In conclusion, we have described the protocol of a prospective, multi-center study of the longitudinal relationship between cognitive dysfunction, severity of depressive (mood) symptoms, and higher-level functional outcomes in Japanese patients with MDD. Results from PERFORM-J should provide valuable information regarding the potential of antidepressant monotherapy to improve symptoms and social functioning in such patients.

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Conflicts of Interest

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Abbreviations

CGI-S: Clinical Global Impression - Severity

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

DSST: Digit Symbol Substitution Test

EQ-5D-5L: EuroQoL 5-Dimensions, 5-levels

MADRS: Montgomery-Asberg Depression Rating Scale

MDD: Major Depressive Disorder

MINI: Mini International Neuropsychiatric Interview

PDQ-5: Perceived Deficit Questionnaire-5 item

PDQ-D: Perceived Deficits Questionnaire-Depression

PHQ-9: Patient Health Questionnaire-9 item

SDS: Sheehan Disability Scale

UPSA-B: University of California, San Diego Performance-based Skills Assessment-Brief

VAS: Visual Analog Scale

WPAI: Work Productivity and Activity Impairment questionnaire

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Protocol

Therapeutic Management of Dyslipidemia Patients at Very High Cardiovascular Risk (CARDIO TRACK): Protocol for the Observational Registry Study

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Abstract

Background: Dyslipidemia is a major modifiable risk factor for atherosclerotic cardiovascular disease. Current South African guidelines recommend titrating lipid-lowering therapy (LLT) to low-density lipoprotein cholesterol (LDL-C) targets stratified by cardiovascular risk. The LDL-C goal for very high-risk patients is <1.8 mmol/L. In international studies, approximately 30% of patients do not achieve this goal despite receiving maximally tolerated statin doses. There is, however, a paucity of data on LDL-C goal achievement in very high-risk South African patients receiving maximal statin doses.

Objective: The goal of the research is to assess LDL-C goal achievement in, and clinical characteristics of, very high cardiovascular risk dyslipidemic patients receiving maximal tolerated statin doses with or without ezetimibe.

Methods: This is an observational, cross-sectional South African registry study that plans to include up to 30 sites and 500 study participants. Adult patients with very high cardiovascular risk status receiving stable, maximally tolerated statin doses (with or without ezetimibe) will be eligible for inclusion.

Results: Funding has been awarded and enrollment began on November 15, 2017, and was completed on April 13, 2018, with 507 participants. Database lock was done on June 21, 2018. The statistical analysis has commenced and we expect the final clinical study report to be completed by October 2018.

Conclusions: This study will document the adequacy of LLT in those at highest risk and will thus fill an important data gap in South Africa. This data may be useful in assessing the need for novel LLTs like proprotein convertase subtilisin/kexin 9 inhibitors that substantially lower cholesterol levels in addition to optimal statin therapy.

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KEYWORDS

dyslipidemia; very high cardiovascular risk; maximally tolerated statin; novel lipid lowering therapy

Introduction

Background

Atherosclerotic cardiovascular disease is a leading contributor to morbidity and mortality in both developing and developed countries [1-3]. Dyslipidemia is an important modifiable risk factor for atherosclerotic cardiovascular disease and was the risk factor with the highest population attributable risk in the INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction) study [4,5].

The prevalence of dyslipidemia in Africa in general and South Africa specifically is increasing and is probably related to lifestyle changes secondary to rapid urbanization [4,6,7]. Patients classified as very high cardiovascular risk are at greatest risk for either new or recurrent major adverse cardiovascular events. The management of major adverse cardiovascular events consumes significant health care resources in addition to imposing a high societal burden due to frequent loss of productivity and need for care. This is particularly concerning in resource-limited settings where there are multitudes of other health priorities including infectious diseases, interpersonal violence, and trauma. Implementing optimal preventative strategies is thus an important priority for health care in South Africa.

In a registry study conducted in a cardiology subspecialty practice in the United States, 30% of 9950 dyslipidemic patients with coronary artery disease were not at low-density lipoprotein cholesterol (LDL-C) goal despite the prescription of what investigators considered optimal lipid-lowering therapy (LLT) [6]. There is a paucity of South African data exploring lipid goal attainment in very high cardiovascular risk patients receiving optimal LLT, here defined as the prescription of maximally tolerated doses of a statin with or without ezetimibe.

South Africa participated in the Dyslipidemia International Study (DYSIS) [8]. The DYSIS study evaluated lipid target attainment in patients treated with statins and also studied variables affecting lipid control. More than 1000 patients were enrolled in the South African arm, and 50.3% were not at their target LDL-C level. Among very high-risk patients, 73.5% were not at target LDL-C. In this group of patients, only 20.2% were on potency level 4 statins or higher (equivalent to at least simvastatin 40 mg/day). Our study will complement the DYSIS South Africa study by further evaluating the very high-risk patients in whom the primary problem is not prescription of an inadequate statin dose.

The South African arm of the International Cholesterol Management Practice Study (ICLPS) (data on file) study [OBS14286] (an international, cross-sectional, observational study to describe management and LDL-C control versus European Society of Cardiology/European Atherosclerosis Society [ESC/EAS] guidelines of patients receiving lipid-modifying treatments in non-US, non-European countries in real-life) showed that 56% of study subjects were classified as very high cardiovascular risk, and 70% of these patients were not at LDL-C goal (data on file). Almost all (99%) study subjects were treated with a statin, but 75% were not receiving

high-intensity statin therapy. The most common reasons participating physicians reported for not escalating patients to higher statin doses were either that they were satisfied with patient's current dose regimen or that there was a cost issue.

The OBS14286/ICLPS study did not include a sufficient number of patients receiving maximum tolerated statin with or without ezetimibe and was thus unable to provide an accurate estimate of the percentage of very high-risk patients not at goal despite aggressive LLT. Additionally, the number of very high-risk patients not at goal despite optimal LLT was not high enough to allow for reliable patient characterization and identification of factors associated with the inability to reach goal.

Rationale

This study will describe and quantify the unmet medical need in very high-risk patients on optimal LLT. This group of patients may benefit either from adding ezetimibe to their statin-based therapy or from the prescription of novel LLTs such as proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors which can lower LDL-C by an additional 50% to 60% on top of statins [9].

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by high concentrations of LDL secondary to defective clearance of LDL by the LDL receptor. FH is highly prevalent in several South African populations secondary to founder effects [10]. Although not all patients with FH are formally classified as very high risk by EAS/ESC guidelines, they were included in this study because many patients with FH are unable to reach target because of their very high baseline LDL-C, and South African guidelines classify FH as a very high-risk condition [6]. FH patients with high LDL-C despite aggressive LLT are also potential candidates for novel therapies.

Definitions

For the purpose of this study, we defined maximum tolerated statin as either the highest licensed dose of a statin or the highest dose that a patient could tolerate. For patients not at LDL-C goal and not receiving the highest licensed dose of either atorvastatin or rosuvastatin, the reason why the dose was not increased to the highest licensed dose or why a more potent statin was not prescribed needed to be well documented. Acceptable reasons for a patient taking a lower statin dose or a low-potency statin included adverse events on higher doses or concomitant medications that may necessitate lower statin doses (eg, colchicine, amiodarone, digoxin, ranolazine, ticagrelor, sacubitril/valsartan). We considered patients who were not at target and who were not receiving maximal doses of either atorvastatin or rosuvastatin and who had no medically valid reason for not up-titrating as not receiving maximal tolerated statin and thus not eligible for this study.

Maximum intensified LLT was defined as a high-intensity statin, either atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily together with ezetimibe 10 mg daily.

Study Objectives

Primary

The primary objective of this study is to assess the percentage of very high cardiovascular risk and FH patients on maximum tolerated statin with and without ezetimibe not reaching LDL-C goal as defined by the ESC/EAS guideline for the management of dyslipidemia in 2016.

Secondary

Secondary objectives of this study are to group patients not at LDL-C goal into those with LDL-C > 5 mmol/L, LDL-C 2.5 to 5 mmol/L, and LDL-C 1.8 to 2.49 mmol/L and to explore and compare characteristics of the subjects grouped according to achieved LDL-C, with a particular emphasis on patients with LDL-C > 5.0 mmol/L. Characteristics to be explored include age, sex, duration of dyslipidemia, obesity, family history of premature atherosclerotic disease, FH diagnosis, diabetes, hypertension, smoking, and use of combination LLT.

Other secondary objectives are to subgroup patients at LDL-C goal into those with LDL-C < 1.8 to 1.0 mmol/L and LDL-C < 1.0 mmol/L; determine the percentage of patients not on ezetimibe despite target LDL-C not being reached; determine reasons for nonuse of ezetimibe in patients not at LDL-C goal (eg, cost, physician choice, medical funder refusing coverage); assess percentage of very high cardiovascular risk dyslipidemia patients on maximum intensified LLTs and still not at LDL-C goal and explore characteristics of the subjects with LDL-C > 5 mmol/L despite maximum intensified LLTs. Characteristics to be explored include age, sex, duration of dyslipidemia, obesity, family history of premature atherosclerotic disease, FH diagnosis, diabetes, hypertension, and smoking.

Methods

Study Design

This is a national, noninterventional, cross-sectional study evaluating LDL-C goal achievement in very high-risk and FH patients receiving maximal tolerated statin therapy. The study will use laboratory data collected during routine care, and no study-specific laboratory investigations will be performed. A single visit coinciding with a scheduled routine medical encounter is planned.

Selection of Patients

Adult patients with very high cardiovascular risk or FH receiving stable maximum tolerated statin therapy for at least 4 weeks

prior to their latest lipid profile are eligible for inclusion. The selection criteria are listed in [Textbox 1](#). We plan to recruit 500 patients in up to 30 centers in South Africa. The minimum patient number is 385 in the stipulated recruitment period of 5 months.

Selection of Investigators

Potential sites will be evaluated by means of a site feasibility questionnaire and, based on the responses received, sites will be selected to participate. Selection criteria include the potential to recruit the required number of patients within the protocol-specified recruitment period and having adequate time and resources to conduct this study.

Statistical Considerations

Determination of Sample Size

Stata software (StataCorp LLC) was used to determine the sample size for this study. It is estimated that a minimum number of 385 patients will provide over 80% power at the .05 significance level to determine the prevalence of patients in South Africa not reaching LDL-C target levels assuming that 50% to 60% are not at target.

Analysis Populations

The analysis population will consist of all patients included in the study who meet all the inclusion criteria and none of the exclusion or withdrawal criteria.

Statistical Methods

Qualitative variables will be described by number of observed values, percentage, and number of missing values (patients with missing data will not be included in the percentage calculation). Quantitative variables will be described by number of observed values, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum as appropriate for the distribution.

Ethical Principles

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly and all subsequent amendments and the guidelines for Good Epidemiology Practice. All necessary submissions (eg, institutional review board/independent ethics committee) will be performed in accordance with local regulations including local data protection regulations. This study has received ethics approval by Pharma Ethics and the University of Cape Town Ethics Committee. Site feasibility and the electronic case report form have been completed.

Textbox 1. Selection criteria.

<p>Inclusion criteria:</p> <ul style="list-style-type: none">• Signed informed consent at enrollment in the study• Adults aged 18 years and older• Patient receiving maximum tolerated dose of statin with or without other lipid-lowering therapy (same drugs and stable doses without interruption) for at least 4 weeks prior the latest lipid profile (or at least total cholesterol and low-density lipoprotein cholesterol) up until study entry• Patient with at least total cholesterol and low-density lipoprotein cholesterol value performed within the past 12 months• At least one of the following criteria is fulfilled:<ul style="list-style-type: none">• Previous acute coronary syndrome (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina)• Coronary revascularization (percutaneous coronary intervention, coronary artery bypass graft surgery, or other arterial revascularization procedures)• Stroke or transient ischemic attack• Peripheral arterial disease as evidenced by history of either intervention, surgery, amputation, or symptoms with low ankle brachial index <0.9• Calculated Systemic Coronary Risk Estimation (Multimedia Appendix 1) $\geq 10\%$ for 10-year risk of fatal cardiovascular disease• Diabetes mellitus with target organ damage such as proteinuria• Diabetes mellitus with another major cardiovascular risk factor such as smoking or hypertension• Definitive familial hypercholesterolemia as per the Dutch Lipid Clinic Network criteria (Multimedia Appendix 2) <p>Exclusion criteria:</p> <ul style="list-style-type: none">• Patient currently participating in a clinical trial, compassionate use program, or extended access program• Patient previously participated in a cholesteryl ester transfer protein or mipomersen clinical trial• Patient previously participated in a proprotein convertase subtilisin/kexin 9 inhibitor trial and low-density lipoprotein cholesterol taken less than 3 months after the last dose of the proprotein convertase subtilisin/kexin 9 inhibitor• Clinician suspects poor adherence to lipid-lowering therapy by patient (eg, patient history of poor attendance of scheduled clinic visits, patient admits nonadherence)• Severe chronic kidney disease (stage IV/V) (ie, estimated glomerular filtration rate <30 mL/min) <p>Withdrawal criteria:</p> <ul style="list-style-type: none">• Withdrawal of informed consent
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Results

Funding has been awarded and enrollment began on November 15, 2017, and was completed on April 13, 2018, with 507 participants. Database lock was done on June 21, 2018. The statistical analysis has commenced and we expect the final clinical study report to be completed by October 2018.

Discussion

Summary

LLT is associated with uniform relative cardiovascular risk reductions across a wide spectrum of patients depending on the LDL-C reduction achieved. However, the absolute risk reduction may vary widely according to baseline absolute risk and LDL-C. The number needed to treat is calculated as 1/absolute risk reduction and is commonly used when evaluating the cost-benefit ratio of novel therapies. Novel and expensive LLT should initially be directed toward patients who have the largest absolute risk reduction and lowest number needed to treat. We

thus focused on identifying and characterizing patients with high absolute baseline risk and elevated LDL-C, including FH patients because of their very high LDL-C levels.

The South African lipid management guidelines [6] vary in some respects from the ESC/EAS guidelines [11]. Specifically, the South African guidelines classify all FH patients, even those without evidence of cardiovascular disease, as very high risk, whereas the ESC/EAS guidelines classify the latter group as high risk. Because of the high prevalence of FH in South Africa, all FH patients are classified as very high risk so that they can all access intensive LLTs in a resource-limited setting.

FH will be identified using the Dutch Lipid Clinic Network (DLCN) criteria. To maximize specificity we will only include patients with a DLCN score of greater than 8 or definitive FH. For study participants who do not have a recorded pretreatment LDL-C level, this will be estimated based on the potency of their current LLT ([Multimedia Appendix 3](#)).

We excluded patients without overt atherosclerotic cardiovascular disease or one of the other very high-risk

indicators but with subclinical atherosclerosis on imaging. This is because these patients probably do not have the same risk as patients who meet the inclusion criteria. Additionally there may be interindividual differences in reporting imaging investigations, especially carotid intima-media thickness assessments.

Patients with severe renal failure are at very high cardiovascular risk, but we excluded them because of the complexity of using LLTs in this group. These patients are frequently prescribed multiple concomitant drugs that may result in drug-drug interactions with statins. Severe renal impairment alters the pharmacokinetics of statins by reducing renal elimination and requires dose reduction to limit deleterious effects including myositis and rhabdomyolysis [12,13]. Furthermore, there is currently no data describing the use of PCSK9 inhibitors in severe renal impairment.

A major challenge was how to exclude subjects who may be nonadherent to pharmacotherapy, as LLT adherence cannot be routinely monitored with drug levels. It is thus best to use other markers that may indicate poor adherence such as poor or incomplete attendance at scheduled clinic visits, failure to refill prescriptions, or patient reported nonadherence. Unfortunately, objectively determining adherence remains challenging and some patients entered into the study may still be non- or incompletely adherent despite the exclusion criteria.

Patients who had previously participated in a cholesteryl ester transfer protein or mipomersen clinical trial were excluded because of the long elimination half-lives of these 2 drugs and the risk of residual effects on the lipid profile.

We excluded patients who had taken a PCSK9 inhibitor within the last 3 months to eliminate the possibility of carry-over effects. PCSK9 inhibitors were not commercially available in South Africa when this study was conceived, and all exposure to such drugs would thus have been either via a clinical trial or compassionate use. It was important not to exclude patients with prior PCSK9 inhibitor exposure as many of these patients would likely be candidates for these drugs once they are commercially available in South Africa.

Limitations

This observational registry study has limitations. Trial sites were conveniently sampled and there may thus be selection bias. This study will largely be done in urban centers at private health care facilities and will thus not be fully representative of the entire South African population.

Conclusion

This study will fill an important data gap by characterizing the highest atherosclerotic cardiovascular disease risk populations in South Africa and providing data on the unmet need for additional LLT.

Acknowledgments

The study was funded by Sanofi and Regeneron.

Conflicts of Interest

PN is Medical Manager, Sanofi South Africa. RM is the former Country Medical Director, Sanofi, South Africa, and current business unit head of Sanofi Genzyme, South Africa. Sanofi and Regeneron manufacture the PCSK9 inhibitor alirocumab. Sanofi markets statins (rosuvastatin and atorvastatin).

Multimedia Appendix 1

Systemic Coronary Risk Estimation.

[PDF File (Adobe PDF File), 81KB - [resprot_v7i6e163_app1.pdf](#)]

Multimedia Appendix 2

Dutch Lipid Clinic Network criteria.

[PDF File (Adobe PDF File), 23KB - [resprot_v7i6e163_app2.pdf](#)]

Multimedia Appendix 3

Drug conversion factors.

[PDF File (Adobe PDF File), 17KB - [resprot_v7i6e163_app3.pdf](#)]

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Abbreviations

DLCN: Dutch Lipid Clinic Network
EAS: European Atherosclerosis Society
ESC: European Society of Cardiology
FH: familial hypercholesterolemia
ICLPS: International Cholesterol Management Practice Study
LDL-C: low-density lipoprotein cholesterol
LLT: lipid-lowering therapy
PCSK9: proprotein convertase subtilisin/kexin 9

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Viewpoint

Workshop on Emerging Technology and Data Analytics for Behavioral Health

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Abstract

Wearable and portable digital devices can support self-monitoring for patients with chronic medical conditions, individuals seeking to reduce stress, and people seeking to modify health-related behaviors such as substance use or overeating. The resulting data may be used directly by a consumer, or shared with a clinician for treatment, a caregiver for assistance, or a health coach for support. The data can also be used by researchers to develop and evaluate just-in-time interventions that leverage mobile technology to help individuals manage their symptoms and behavior in real time and as needed. Such wearable systems have huge potential for promoting delivery of anywhere-anytime health care, improving public health, and enhancing the quality of life for many people. The Center for Technology and Behavioral Health at Dartmouth College, a P30 “Center of Excellence” supported by the National Institute on Drug Abuse at the National Institutes of Health, conducted a workshop in February 2017 on innovations in emerging technology, user-centered design, and data analytics for behavioral health, with presentations by a diverse range of experts in the field. The workshop focused on wearable and mobile technologies being used in clinical and research contexts, with an emphasis on applications in mental health, addiction, and health behavior change. In this paper, we summarize the workshop panels on mobile sensing, user experience design, statistics and machine learning, and privacy and security, and conclude with suggested research directions for this important and emerging field of applying digital approaches to behavioral health. Workshop insights yielded four key directions for future research: (1) a need for behavioral health researchers to work iteratively with experts in emerging technology and data analytics, (2) a need for research into optimal user-interface design for behavioral health technologies, (3) a need for privacy-oriented design from the beginning of a novel technology, and (4) the need to develop new analytical methods that can scale to thousands of individuals and billions of data points.

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KEYWORDS

behavioral health; mobile technology; wearable devices; data analytics; mHealth

Introduction

Digital technologies offer unprecedented opportunities to better understand and enhance behavioral health—individuals’ cognitive, emotional, and behavioral well-being. Behavioral

health includes areas of substance use and mental health, and also embraces a broader spectrum of behavior (such as diet, physical activity, medical regimen adherence, and other lifestyle factors) which may impact individuals’ quality of life and health outcomes. Given the widespread access to technology

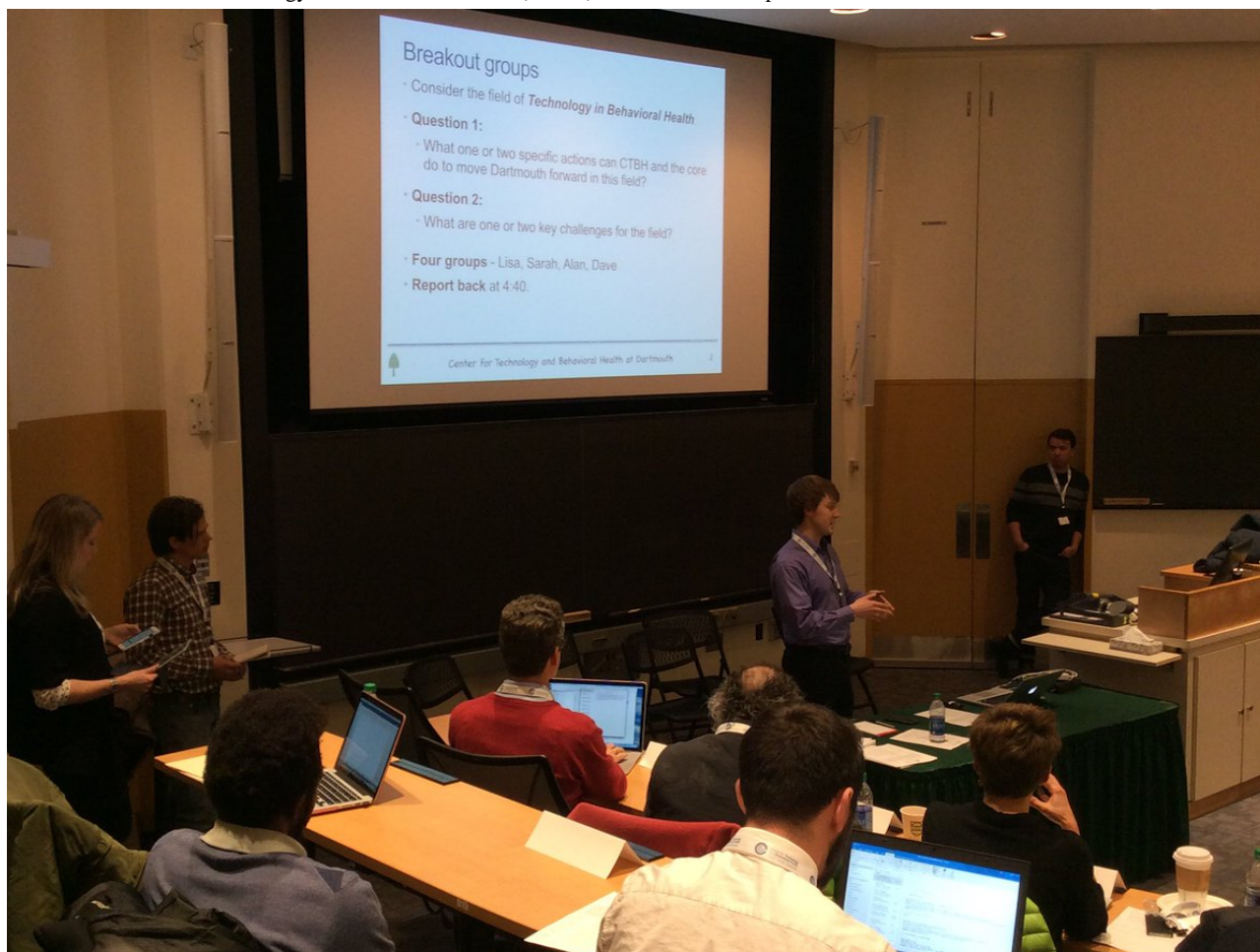
worldwide, health monitoring and behavior change tools delivered on mobile platforms enable widespread reach and scalability of evidence-based interventions.

The rapidly evolving interdisciplinary field of behavioral health is making increased use of emerging technologies, novel methodologies, and data analytics in the development of effective and personalized digital therapeutic interventions. These technologies include mobile and wearable devices, and enable the delivery of personalized, “in the moment” interventions to empower patients and improve health. Novel sensing technologies allow for real-time measurement of a range of physiological, behavioral, and social activities and can help inform optimal timing of delivery of mobile interventions. Social media can be harnessed for rich data mining to develop a deeper understanding of both individual and population-level trends in health behavior and can serve as novel platforms for the delivery of behavior-change interventions. Increasingly sophisticated data analytics can be used to gain insights from mobile, sensor, and social data about individual and population health via advanced statistical methods, including machine learning and predictive modeling. Collectively, these digital technologies enable an entirely new offering of tools for collecting rich data about individuals’ behavior, health, and environment, provide personalized interventions and resources based on individuals’ needs and preferences, and enable dynamic

statistical models and computational methods to predict and characterize individuals’ changing needs and health trajectories over time.

The Center for Technology and Behavioral Health (CTBH, a P30 “Center of Excellence” supported by the National Institute on Drug Abuse at the National Institutes of Health) is an interdisciplinary research center at Dartmouth College focused on the use of scientific methods to inform the optimal development, systematic evaluation, and sustainable implementation of a wide array of digital therapeutic tools for behavioral health (including web and mobile tools to help individuals manage challenges such as substance use and mental-health disorders and to promote health behavior change) [1]. In February 2017, CTBH sponsored a workshop on innovations in emerging technology, user-centered design, and data analytics for behavioral health, with presentations by a diverse range of experts in the field. Although all of the attendees and speakers were from Dartmouth, the insights from the workshop experience are broadly applicable. This paper summarizes the workshop panels on mobile sensing, user-experience design, statistics and machine learning, and privacy and security, and concludes with suggested research directions for this important and emerging field of applying digital approaches to behavioral health.

Figure 1. The Center for Technology and Behavioral Health (CTBH) Feb 2017 workshop.



Mobile Sensing

David Kotz (Computer Science) observed that trends in health care information technology are leading to increased interest in monitoring of patients outside the clinical setting, through wearable and location-based, at-home technologies. He provided his own working definition of “mobile health”, or mHealth, as “the use of mobile computing and communications technology in the delivery of health care or collection of health information,” giving examples ranging from clinical to home use of mobile devices, to personal wellness apps, to opportunities for mHealth in the developing world.

Three other speakers described specific opportunities for mobile sensing in behavioral health. Ryan Halter (Engineering) described four projects underway at Dartmouth, beginning with Amulet [2,3], a collaborative effort to develop a wearable computing platform that can run multiple mHealth apps with strong security guarantees and weeks-long battery life. In a related project, Halter’s group is developing a wristband to measure electro-dermal activity which, in combination with the Amulet and a chest-strap heart-rate monitor, they use to measure stress in free-living conditions. Kofi Odame (Engineering) spoke about his work in ultra-low-power analog electronics, for example, in measuring wheezing, coughing, and related sounds from a wearable microphone. In a new project, Auracle [4], Halter, Odame and Kotz are developing an ear-worn device that can detect eating, in support of eating-behavior studies. They are also developing a method for bioimpedance-based cardiorespiratory monitoring, an array of electrodes worn around the chest and waist that provides real-time images of cardiac and lung function. Finally, Bill Kelley (Psychological and Brain Sciences) spoke about his use of smartphone sensing for a months-long study of student dysphoria, depression, and mental health in free-living conditions. They found strong correlations between the data from passive smartphone sensing with self-reported (Ecological Momentary Assessment; EMA) [5] responses and clinical instruments such as Patient Health Questionnaire-9 (a standardized measure of depressive symptoms) [6].

All the speakers expressed great optimism for the future of wearable and mobile sensing technology, bringing new insights into behavioral health and new opportunities for effective interventions, while noting significant research challenges ahead.

User Experience Design for Behavioral Change and Health

The ease of use and aesthetic qualities of innovations, such as digital therapeutic interventions, are critical to successful dissemination and implementation of such innovations [7,8]. Presentations in this session tackled the important topics of user-interface (UI) and user-experience (UX) design for development of innovative, engaging, and effective digital approaches to behavior change and health. Sarah Lord (Psychiatry and Pediatrics) raised three key questions for panelists: (1) What are the best practices guiding UI/UX for digital approaches to behavioral health? (2) What are the

common challenges to effective UI/UX and effective solutions to overcome those challenges? (3) How can we foster a common language among interdisciplinary teams to facilitate a successful UI/UX process for digital therapeutics for behavioral health?

Craig Ganoë (Data Science) provided a brief history of the field of human-computer interfaces and UI/UX, from early engineering emphasis on system performance to current iterative participatory design and development approaches. Ganoë highlighted consideration of the task-artifact cycle [9], emphasizing that assessment of UI/UX throughout the research process will yield the most effective products.

Lorie Loeb (Computer Science) noted that effective UI/UX promotes motivation through appeal to both emotional and intellectual aspects of individuals and presented case examples to demonstrate effective UI/UX of digital approaches for behavior change. In one case, college students worked iteratively with researchers to design and develop a simple, colorful, engaging kiosk to elicit stress assessment by college students. A 2-week pilot of the kiosk in a high traffic area of the college library yielded over 8000 responses, and positive feedback by students (personal communication by Sarah Lord, October 2017). In another case, Loeb used animation (of polar bears struggling with climate change) and data visualization (of dormitory energy-use data) and found increased energy conservation among college students [10].

Xing-Dong Yang (Computer Science) highlighted cutting-edge basic research focused on interaction techniques with wearable devices. Yang demonstrated an early prototype of a smartwatch face that orbits on the wristband, allowing for ready access to the watch features at any time with minimal intrusion [11]. Yang emphasized the potential of such technology for improving the lives of those with physical disabilities.

Statistics, Machine Learning, and Data Analytics

Informatics and data analytics play an increasingly important role in understanding behavior, designing behavioral interventions, and interpreting data from behavior-related sensors. James O’Malley (Data Science) noted that just a few decades ago there was a sentiment among academic statisticians that “the best statisticians do not work with data,” a reflection of the focus on independent theoretical and methodological work in promotion criteria for tenure-line university-based statisticians and biostatisticians. The computing evolution has led to a reversal of priorities, with data extraction, manipulation, analysis, and presentation all deemed highly important.

Three panelists spoke about the role of mobile phone and other emerging technologies in their behavioral-health research. Emily Scherer, a biostatistician, described how the already-broad skillset of a biostatistician has changed due to a need to use or develop more complex analytic approaches and data gathering or acquiring techniques (eg, web-scraping) than those used in traditional randomized clinical trials and other common statistical domains or problems. For example, EMA data is an increasingly useful form of intensive longitudinal data [5]. Although EMA data is becoming commonplace due to smart

devices that enable in-context monitoring of participants and adaptive interventions on patients, methods for analyzing these data are in their infancy. Scherer is leading several new lines of research, including the use of penalized functional regression modeling to identify the critical windows of time in which a patient's mental health status is changing the most [12].

Saeed Hassanpour (Data Science) and *Benjamin Crosier* (Data Science) presented research characterized by large, complex, and unbalanced data sets. Hassanpour, an expert in natural-language processing, uses novel algorithms for reducing text and imaging data to forms that Crosier, an expert in quantitative social psychology, can use. They use Instagram location and network data to assess the impact of social media on a patient's behavioral risk. They also use deep learning and convolutional neural networks to identify recurring patterns in data and classify observations or participants into groups and use other machine-learning methods to develop prediction rules often without using fully-specified statistical models.

All three—Scherer, Hassanpour, and Crosier—benefit from “Big Data” generated from enhanced monitoring capabilities, electronic medical records, high-throughput technologies, and networked research resources.

Privacy and Security

Privacy and security are central problems for many digital apps, and as *David Kotz* (Computer Science) observed, several trends in information technology development make privacy and security concerns in health care especially acute. These trends include the need for accountable care and patient engagement, and continuous patient monitoring outside the clinical setting. Emerging threats and a changing regulatory environment further emphasize the importance of security and privacy in all digital technologies in health care settings.

mHealth technologies, enabled by the advent of mobile devices and cloud services for health-related apps, present an additional set of challenges. Given the immediate, personal impact of these devices, security and privacy concerns are even more acute. mHealth devices directly affect users' health or health decisions, and mHealth data are inherently personal and thus highly sensitive. In addition, mHealth apps collect longitudinal data, including behavioral information, from a broad range of lifestyle activities—data which have the potential to be analyzed to produce insights about mood and personality. Perhaps most concerning, the mHealth sector encompasses a broad range of apps unbound by specific regulations protecting health data privacy. As witnessed by the recent controversy over Cambridge Analytica's psychographic analysis of illicitly-obtained Facebook user data, these matters are increasingly matters of extreme societal concern.

Kotz, joined by *Denise Anthony* (Sociology) and *Luke Stark* (Sociology) discussed some of the central questions around privacy, security, and the broader social use of mHealth technologies, including the growing field of applications focusing on substance use and mental health. Key questions highlighted for future exploration included identifying what laws, policies, regulations and guidelines are currently in place

to shape the technical developments around privacy and security in mobile health, and whether they were adequate for technical developments in the field; and what determining what kind of research was being conducted on the empirical impact of mobile health devices, particularly as related to their privacy affordances and security vulnerabilities. The three also discussed how human factors in UI/UX design, especially work on privacy-preserving or enhancing technologies and the broader tenets of privacy by design, could be part of the solution to the privacy and security concerns with mobile devices, and which laws and regulations might need modification to align with the privacy and security affordances of mobile-health technologies.

Conclusions and Recommendations

The day-long multidisciplinary workshop left attendees feeling energized and excited about the potential for emerging technologies and data analytics to bring new insights to behavioral health, and new opportunities for innovative interventions. A few of the insights and recommendations from the presentations and conversation at the workshop are listed below.

Wearable devices bring new opportunities for sensing, computation, and interaction, with potential far beyond the capabilities of today's fitness trackers and smartwatches. Sensor-design engineers should work closely with behavioral health scientists to understand what information would be most insightful, and seek innovative, unobtrusive mechanisms to collect that information.

Many behavioral-health studies (or interventions) use wearables, smartphones, and Web portals to interact with participants (or patients)—and yet, it remains a challenge to design interfaces that are efficient, effective, acceptable, and usable by target populations. Indeed, without careful thought to the user experience, including physical design of wearable devices and the user's interaction with physical or digital interfaces, otherwise-innovative technologies may not be effective, or even adopted. Behavioral-health scientists and UI/UX designers should work collaboratively when developing technology-based interventions, and ideally with iterative input from representatives of the intended target end-users of the intervention.

New technologies can produce enormous amounts of data, rich with potential for insights into human behavior but require new approaches to analysis. Studies may involve hundreds, thousands, or even tens of thousands of participants—and billions of data points—requiring the application of innovative approaches in statistical methods, machine learning, and data analytics. Health researchers and data scientists should collaborate to bring new approaches to these rich new data sources.

Privacy should be a key factor in the design of all behavioral-health technologies, from conceptualization through prototyping and potential commercialization. Numerous design principles and heuristics, most notably those of privacy by design, are available as resources in these endeavors. Consistent with these design principles, designers and researchers should

seek effective means to communicate to the end-user about what data is being collected, how it will be used, who will have access, and how it can be disposed. Poor attention to privacy may impede adoption, especially in a global regulatory context, now including the European Union's General Data Protection Regulation, whereas strong privacy protections can encourage adoption among sensitive populations.

Mobile technologies can collect a wide range of data about individuals, including types of data not traditionally considered to be protected health information or personally identifiable information, but which (with modern analytic methods) can

extract insights about sensitive behaviors and even reidentify anonymous individuals. Technology developers should limit data collection to only that which is needed, avoid transmitting and storing raw sensor data, and put strong technical and administrative controls on secondary use of data.

The Center for Technology and Behavioral Health at Dartmouth, as a community of researchers from sensor engineering, computer science, data analytics, psychiatry, and behavioral health, is poised to pursue these opportunities, and encourages researchers everywhere to engage with these exciting challenges.

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Conflicts of Interest

DK, SEL, AJOM, and LS have no conflicts of interest. LAM is affiliated with Square2 Systems, Inc, HealthSim, LLC, and Pear Therapeutics. These relationships are extensively managed by LAM and her academic institution.

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Abbreviations

CTBH: Center for Technology and Behavioral Health

EMA: ecological momentary assessment

mHealth: mobile health

UI: user interface design

UX: user experience

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Corrigenda and Addenda

Metadata Correction: Uterine Fundectomy in Patients with Benign Etiology Undergoing Hysterectomy: New Surgical Technique

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The authors of the paper "Uterine Fundectomy in Patients with Benign Etiology Undergoing Hysterectomy: New Surgical Technique" (*JMIR Res Protoc* 2017;6(19):e150) regret that an error occurred in the listing of some affiliation addresses in their original paper and would like to apologize for any inconvenience caused.

The correct listings are as follows:

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The corrected article will appear in the online version of the paper on the JMIR website on June 28, 2018, 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 re-submitted to those repositories.

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Original Paper

Identification of Implementation Strategies Used for the Circle of Security-Virginia Family Model Intervention: Concept Mapping Study

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Abstract

Background: A reoccurring finding from health and clinical services is the failure to implement theory and research into practice and policy in appropriate and efficient ways, which is why it is essential to develop and identify implementation strategies, as they constitute the *how-to* component of translating and changing health practices.

Objective: The aim of this study was to provide a systematic and comprehensive review of the implementation strategies that have been applied for the Circle of Security-Virginia Family (COS-VF) model by developing an implementation protocol.

Methods: First, informal interviews and documents were analyzed using concept mapping to identify implementation strategies. All documentation from the Network for Infant Mental Health's work with COS-VF was made available and included for analysis, and the participants were interviewed to validate the findings and add information not present in the archives. To avoid lack of clarity, an existing taxonomy of implementation strategies, the Expert Recommendations for Implementing Change, was used to conceptualize (ie, name and define) strategies. Second, the identified strategies were specified according to Proctor and colleagues' recommendations for reporting in terms of seven dimensions: actor, the action, action targets, temporality, dose, implementation outcomes, and theoretical justification. This ensures a full description of the implementation strategies and how these should be used in practice.

Results: Ten implementation strategies were identified: (1) develop educational materials, (2) conduct ongoing training, (3) audit and feedback, (4) make training dynamic, (5) distribute educational materials, (6) mandate change, (7) obtain formal commitments, (8) centralize technical assistance, (9) create or change credentialing and licensure standards, and (10) organize clinician implementation team meetings.

Conclusions: This protocol provides a systematic and comprehensive overview of the implementation of the COS-VF in health services. It constitutes a blueprint for the implementation of COS-VF that supports the interpretation of subsequent evaluation studies, facilitates knowledge transfer and reproducibility of research results in practice, and eases the replication and comparison of implementation strategies in COS-VF and other interventions.

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KEYWORDS

implementation strategies; Circle of Security Virginia-Family Model; Expert Recommendations for Implementing Change taxonomy; methodology; reproducibility; knowledge transfer

Introduction

Background

Using interventions that aim to change health provider behavior can be an effective way of improving health outcomes and reducing health costs [1]. At the same time, one of the most consistent findings from research on health and clinical services is the failure to implement theory and research into practice and policy [2] and sustain the use of interventions and their effects in practice [3]. Therefore, several researchers argue that there is an urgent need for methods of specifying and reporting interventions in ways that strengthen the knowledge base necessary to enable interventions to be more effective, replicable, and implementable (see eg, [4-6]).

There are several barriers that hamper successful implementation of innovations. A lack of conceptual clarity, for example, has made it difficult to identify, develop, and test implementation strategies. First, the terms and definitions for implementation strategies are used inconsistently. Second, the description for implementation strategies are not detailed enough to enable scientific or real-world replication, which is one of the basic premises of research [7]. This has until recently, partly been because of a lack of reporting guidelines for implementation studies and strategies (for recent standards, see [8]). Thus, essentially, the way in which intervention research is reported, generally fails to contribute toward a cumulative science of interventions. Other problems that occur is that implementation strategies are rarely justified theoretically, they either lack operational definitions or manuals to guide their use, or are part of a multifaceted, packaged approach whose specific elements are poorly understood [5]. It also obscures the interpretation and understanding of outcomes in intervention studies. On the one hand, with ineffective interventions, it becomes practically impossible to know whether it was the intervention itself that failed, the way it was integrated in practice, or both. On the other hand, it is difficult to understand how to integrate and embed a presumably effective intervention into practice without systematic and comprehensive protocols for their implementation.

The significant gap between what we know and what we do (ie, the “how-to” when translating research findings into daily practice) challenges effective and efficient health care services [9], which is why much of the scientific literature emphasizes the need to understand the barriers to delivering optimal health care and applying research into practice. To bridge this gap, it is our belief that implementation protocols should be routinely published for all interventions, in a similar way as study and intervention protocols. This will contribute to accumulate and extend the evidence-base for intervention and implementation

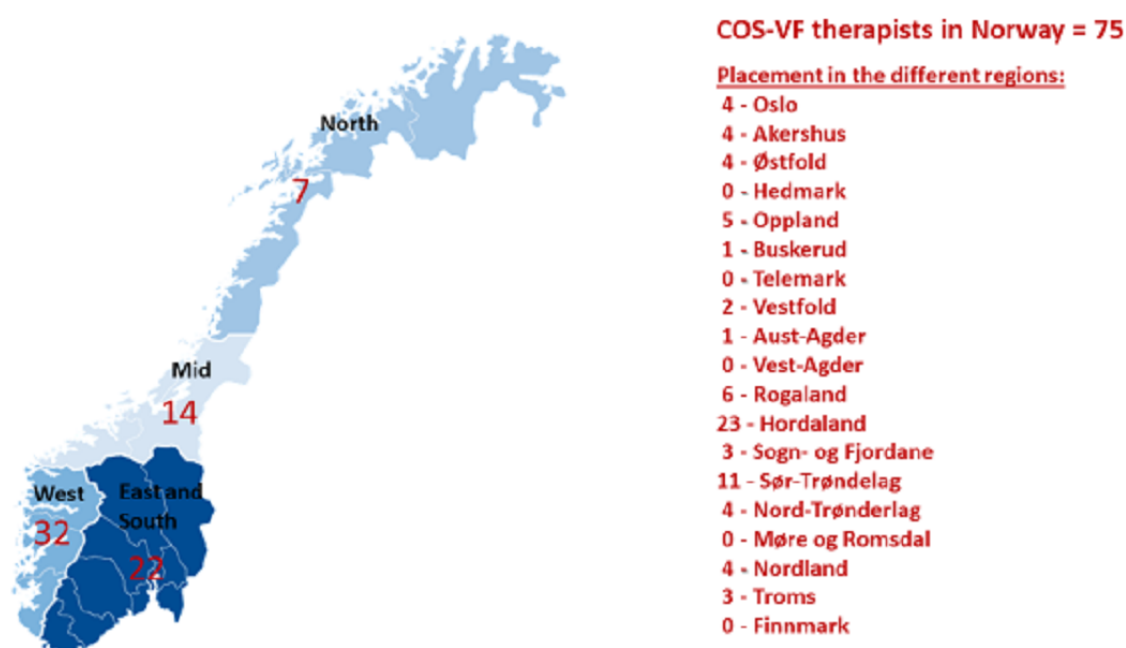
research and improve future decisions regarding the implementation of interventions among policy and decision makers, health services, practitioners, and other stakeholders (eg, determining whether implementing an intervention into existing practice is feasible and acceptable). Furthermore, as research resources are finite, implementation protocols will also help the scientific community avoid unnecessary and duplicate research because of inconsistencies in language or inadequate descriptions. By clearly specifying and reporting strategies used to embed an intervention into practice, it will also ease the interpretation of research findings and contribute to research syntheses (eg, systematic reviews and meta-analyses).

Circle of Security-Virginia Family Model

The Circle of Security-Virginia Family (COS-VF) model is an intervention developed for primary caregivers (eg, biological parents, foster parents, and adoptive parents) with children who have or are at risk of developing attachment problems [10]. COS-VF is designed to intervene in areas related to caregiver-child relationships; attachment, exploration, behavior management, and emotion-regulation. The core constructs involve Bowlby [11] and Ainsworth's [12] ideas of a Secure Base and Safe Haven, and the purpose is to convey these ideas to caregivers in a way that is tangible, as well as easy to practice in their daily life. The treatment follows a manual that is divided into six different phases: (1) families are assessed and a treatment plan is prepared, (2) establishing a safe base when working toward change, (3) learning the COS-VF framework, (4) developing observation abilities, (5) increasing the caregivers reflective functioning, and (6) empathic shift, assessment of change, and end of treatment. Each phase has different goals for learning, and the therapists evaluate how long it takes to acquire learning goals in the different phases for each individual family. It is often 20 to 30 hours before the entire manual has been reviewed and the change targets have been reached.

The Network for Infant Mental Health (NIMH) in Norway, which is responsible for training and implementation of interventions in the field of infant mental health, established a collaboration with Robert Marvin and William Whelan (ie, COS-VF developers) in 2009 to learn the COS-VF intervention. The goal was to gradually take complete responsibility for the COS-VF training and supervision in Norway. This was a stepwise educational process where a group of clinical psychologists at NIMH, first, became certified in using the Secure Base-Safe Haven coding system (SBSH-CS; Marvin and Whelan, unpublished data, 2007 [13]) for the Strange Situation Procedure (SSP, [12]), then as COS-VF therapists, then as COS-VF supervisors and, finally, as teachers for future COS-VF therapists. The current state of the implementation in Norway is depicted in Figure 1.

Figure 1. The current state of the implementation of Circle of Security-Virginia Family (COS-VF) model in Norway.



Clinical manuals and instructions on how to use the materials in the intervention were provided, but there were no manuals or instructions on how to implement the intervention in an effective way in clinical settings. The COS-VF providers at NIMH used the core implementation components proposed by Fixsen and Blasé [14] (ie, recruitment and selection, pre- and in-service training, consultation and coaching, staff evaluation, decision support data systems, facilitative administrative supports, and systems interventions) informally to implement COS-VF in the best possible way. This is because core implementation components are “by definition, essential to achieving good outcomes for those targeted by the intervention” [15]. However, no formal implementation plan was ever designed (ie, much remained tacit knowledge), and thus far, there is still no formal implementation protocol that can facilitate the implementation process for either COS-VF providers or COS-VF therapists in Norway or internationally.

To our knowledge, there is no published research on COS-VF to date. However, the core components in COS-VF are similar to the content of the original 20-week, group-based COS protocol that has shown promising results in quasi-experimental studies (see, eg, [16-18]), with the more recent addition of a small randomized trial that demonstrated its effectiveness on preschool children’s attachment and well-being [19]. The main differences between the intervention protocols are its group-based format and focus on caregivers’ core sensitivities, whereas COS-VF therapists work with individual families, focusing on strategies used to navigate close relationships and protect caregivers from emotional distress. Moreover, there are several other versions of COS (eg, COS-Parenting and the COS Virginia-Group model), and training in these interventions is offered both in Norway and internationally, which is yet another reason there is a need for an implementation protocol that clearly describes the different ways in which these are implemented in health and clinical services. The aim of the study was, therefore,

to provide a systematic and comprehensive review of the implementation strategies that have been applied for COS-VF by developing an implementation protocol.

Methods

Protocol Development

This study is part of a larger project investigating the implementation of COS-VF in Norway. The first step in this process was to develop an implementation protocol for the intervention, which commenced by identifying implementation strategies, defined as “methods or techniques used to enhance the adaption, implementation and sustainability of a clinical program or practice” [5], but more easily understood as the *how-to* component of innovation in health care. The second step was to use Proctor and colleagues’ [5] recommendations for reporting, which are the fundamental principles of *naming*, *defining*, and *specifying or organizing* implementation strategies (also see Analysis below).

Participants

The main work and data in this study consisted of analyzing all the documents in the COS-VF archives. Moreover, to validate the findings, we (ie, BN and FD) conducted interviews with two of the key personnel involved in the implementation of COS-VF; ie, one COS-VF supervisor and one staff member at the NIMH, who provide technical and administrative support to COS-VF therapists. The number of COS-VF supervisors and administrative staff is very limited; only six supervisors and one staff member are involved with technical and administrative support. However, a very knowledgeable supervisor was interviewed. The supervisor lived in the same city as the researchers (which facilitated ongoing contact and meetings) and was one of the first in Norway to become certified as a COS-VF therapist and supervisor, and thus, has extensive experience with the intervention.

Procedure

At first, the researchers (BN and FD) were provided with access to the archives at NIMH that contain all the information and documentation concerning COS-VF. In parallel, informal interviews were used to help identify key implementation strategies in COS-VF. Informal interviews do not use a prepared set of interview questions, rather they have a repertoire of questions they draw upon when appropriate [20]. In this study, the repertoire was theory-driven, based on the core implementation components proposed by Fixsen and colleagues [21], although the analysis was conducted independent from their model. While working with identifying strategies and describing them, the researchers (BN and FD) were in ongoing contact with the participants to acquire further information when needed or revise the preliminary mapping of implementation strategies. Finally, participants were asked to review the final results of the analysis to make sure all central strategies were identified and correctly described.

Analysis

All documents concerning COS-VF in the NIMH database were analyzed by means of concept mapping, to identify a distinct set of implementation strategies and their interrelationships. In this study, conceptual mapping refers to a specific integrated approach of concept mapping, described as “a structured methodology for organizing the ideas of a group or organization, to bring together diverse groups of stakeholders and help them rapidly form a common framework that can be used for planning, evaluation, or both” [22]. This approach facilitates collection of information from different participants and other data sources in practically any scenario in which an issue or need requires definition, planning, and evaluation and enables feedback on these data to participants in a timely manner.

First, all of the documents or materials in the archives were carefully reviewed and manually organized based on whether they were relevant to implementation or not. There were 104 items (ie, emails, Word or PDF documents, video materials, and pictures) in the archives, only 21 one of which were used in the analysis. These items included (1) NIMH’s emails sent to the students about the educational program and the NIMH’s cloud service (will be further explained in the Results section), (2) descriptions of the educational program, (3) educational certificates for therapists and supervisors, (4) descriptions of the core sensitivities revised and adjusted for Norwegian conditions, (5) instructions for the SSP, (6) transcription templates (for transcribing SSP), (7) overview of videos to use during lectures and for certification, (8) confidentiality agreements (all of the mentioned items were developed by the NIMH), (9) the COS interview (developed by Bert Powell et al), (10) the SBSH-CS (developed by Bob Marvin and William Whelan), and (11) the certification criteria (developed by Bob Marvin, William Whelan, and the NIMH). BN and FD also got access to the NIMH’s cloud service where there were 20 SSP training videos (ie, of families in the SSP) and given the printed COS-VF manual (developed by Bob Marvin and William Whelan; translated into Norwegian by NIMH). The other items in the archives were excluded because they were either irrelevant for the implementation, old versions (new ones were available),

or duplicates. None of the items used for the implementation were peer-reviewed.

As we were following Proctor and colleagues’ [5] guidelines for specifying and reporting implementation strategies, the next step was to identify and name the strategies involved in the COS-VF implementation. *Naming* refers to a process of labeling a strategy, preferably using language that is consistent with existing literature. To support this process, we applied the Expert Recommendations for Implementing Change (ERIC: [7]) taxonomy to identify and name the unique implementation strategies. Each of the documents or materials in the archives was organized based on where they belonged within the different strategies in the ERIC taxonomy. After all of the documents or materials had been categorized, the participants were interviewed to verify that the different documents or materials BN had categorized and described were done so correctly, and furthermore, to give additional information about the implementation process that could not be identified by going through the archives. After the findings had been validated and the different strategies were identified, the next step in Proctor and colleagues’ [5] guidelines was to define and organize the implementation strategies. *Defining* is conceptually describing what the strategy involves, whereas *organizing* entails operationalization of the core strategies according to seven dimensions: (1) the actors (ie, who delivers the strategy), (2) the actions (ie, what will be done), (3) action targets (ie, toward what or whom and at what level), (4) temporality (ie, when or in what phase), (5) dose (ie, at what frequency and intensity), (6) implementation outcome(s) affected, and (7) justification (ie, theoretical, empirical, or pragmatic justification).

Proctor and colleagues’ [23] taxonomy of implementation outcomes was used to label implementation outcomes (ie, dimension 6) to make sure there was clarity concerning the terms used to describe these. This taxonomy consists of the following implementation outcomes: (1) acceptability (ie., the belief that the innovation is agreeable, palatable, or satisfactory), (b) adoption (ie, the decision, intention, or action to try and employ the innovation), (c) appropriateness (ie, the perceived suitability, applicability, or compatibility of the innovation), (d) feasibility (ie, the extent to which the innovation can be carried out), (e) implementation cost (ie, the cost impact of the implementation effort), (f) penetration (ie, the way a practice is integrated within service settings and its subsystems), and (g) sustainability (ie, the way the innovation is maintained within the organizations ongoing operations).

A concept map was designed to conceptualize how the different strategies were related to each other. As a last step, the implementation strategies were organized within Fixsen and Blasé’s [14] diagram of core implementation components, as they were the inspiration for the NIHM’s implementation process. The participants were given access to the result section to validate and give feedback on all of the results before the implementation protocol was submitted for publication.

Post-Hoc Application

Ideally, an implementation protocol should be developed during the planning stage of an intervention; however, it can also be developed in a reflective or evaluation phase, as in this study,

which is an important part of the implementation. Several implementation theories such as Fixsen's [24] Active Implementation Framework (AIF), the Dynamic Adaptation Process model [25], and Consolidated Framework for Implementation Research model [26] acknowledge the importance of evaluation and reflective phases in continuous cycles of quality improvement. Implementation theories such as the AIF framework were used informally to plan the implementation of COS-VF, thereby making a post-hoc implementation protocol both feasible and informative. A systematic and comprehensive implementation protocol can help identify, synthesize, and critically appraise the implementation of an intervention and help prevent "type III" errors (ie, correctly rejecting the effectiveness of an intervention when the intervention was inadequately implemented or delivered; [27]). Thus, it is better to develop an implementation protocol post-hoc, rather than never. This may contribute to identifying potential improvements to the continued implementation of COS-VF (or other interventions) and understanding of subsequent research results. More generally, it may also contribute to documenting practical implementation of interventions in health care services and provide "lessons learned" for researchers, clinicians, and decision makers (eg, when to use the same implementation strategies or devise new strategies), especially when viewed conjointly with results from evaluation studies.

Results

Implementation Strategies

After analyzing all the documents and information received from participants, we were able to identify 10 implementation strategies from the ERIC taxonomy [7] that are present in the implementation of COS-VF (see Table 1).

After implementation strategies were identified, named, and defined, they were organized according to Proctor and colleagues' [5] seven dimensions (see Tables 2 and 3). The strategies and their interrelationships are depicted in Figure 2.

Develop Educational Materials

Before onset of therapist training in COS-VF, different educational materials were developed (ie, SBSH-CS and the COS-VF intervention manual) to train new therapists to a certain competency level and ensure intervention fidelity (see Table 2 and Figure 2). The use of manuals also facilitates replications by different researchers and increases comparability across studies using the same manuals [28]. Supervisors in Norway developed a Norwegian version of the COS-VF manual [29], which is the version currently used in Norwegian health and clinical services. This manual consists of six phases designed to guide therapists in (1) Assessment and treatment planning, (2) Establishing a supportive environment, (3), The didactics of the COS, (4) Building parents' observation skills, (5) Increasing parental reflective functioning, and (6) Practice and integration. Manuals are distributed to trainees and form the basis for intervention delivery, fidelity, and certification criteria (see below).

Distribute Educational Materials

Clinicians in training receive access to all educational material via a cloud storage solution. This requires that trainees have a computer or laptop at their place of work that has access to the cloud service. Personnel at NIMH distribute educational materials online (eg, SSP training videos), provide technical support, and convey information concerning the training (see Table 3 and Figure 2).

Table 1. Implementation strategies identified in the Circle of Security-Virginia Family model.

Strategy	Definition
Develop educational materials	Develop and format manuals, toolkits, and other supporting materials in ways that make it easier for stakeholders to learn about the innovation and for clinicians to learn how to deliver the clinical innovation.
Distribute educational materials	Distribute educational materials (including guidelines, manuals, and supportive materials) in person, by mail, and electronically.
Conduct training	Plan for and conduct training in the clinical innovation in an ongoing way.
Make training dynamic	Vary information delivery methods to cater to different learning styles and work context, and shape the training in the innovation to be interactive.
Audit and feedback	Collect clinical performance data over a specific time period and give it to supervisors to evaluate and modify behavior.
Create or change credentialing and licensure standards	Create an organization that certifies clinicians in the innovation or encourage an existing organization to do so. Change governmental professional certification or licensure requirements to include delivering the innovation. Work to alter continuing education requirements to shape professional practice toward the innovation
Organize clinician implementation meetings	Develop and support teams of clinicians who are implementing the innovation, and give them protected time to reflect on the implementation effort, share lessons learned, and support one another's learning
Obtain formal commitments	Obtain written commitments from key partners that state what they will do to implement the innovation.
Mandate change	Have leadership declare the priority of the innovation and their determination to have it implemented.
Centralize technical assistance	Develop and use centralized system to deliver technical assistance focused on implementation issues.

Table 2. Specifications of strategies used to implement the Circle of Security-Virginia Family model in health care services.

Strategy	Develop educational materials	Distribute educational materials	Conduct ongoing training	Make training dynamic	Audit and provide feedback
Actor(s)	Developers (United States) and supervisors	Developers (United States), supervisors, and technical support worker (NIMH ^a)	Supervisors	Developers (United States) and supervisors	Supervisors
Action	The developers developed a COS-VF ^b manual (Marvin and Whelan, 2010) and a Secure base-safe haven coding system (SBSH-CS, Marvin and Whelan, 2007) for the Strange Situation Procedure (SSP) that the therapists use during training and as part of the treatment after certification	Provide the clinicians with the information and materials they need to complete their COS-VF training, that is, the COS-VF manual, the SBSH-SC, as well as the practice SSP videos which are provided online	Training in attachment theory and observation of caregiver-child dyads based on the SSP (Ainsworth, 1968), the COS-VF manual, and measurements (ie, coding the SSP and COS interview)	The training provides knowledge through lectures on attachment theory and caregiver-child interaction, as well as real-life examples from SSP videotapes. Furthermore, the training allows the clinicians to practice their skills and get feedback from supervisors to enable them to attain the necessary competence	It is expected that the therapists complete the intervention with two caregiver-child dyads under supervision when working toward certification. The therapist should demonstrate appropriate skills in implementing all six phases of the intervention across the two cases
Target action	Therapists, clinicians in training	Clinicians in COS-VF training	Clinicians with a minimal of 3 years of college education within health and social sciences	Clinicians in training	Clinicians in training
Temporality	The COS-VF manual and the SBSH-CS were developed before the intervention was implemented	When they start section two of their educational course	Training starts before the intervention is implemented and lasts approximately 2.5 years	Ongoing	Audit and feedback begins when the clinicians start working with cases or families under supervision
Dose	The therapist and the clinicians in training use the manuals as part of the therapy with every case or family	They only receive educational materials once during their training	The educational course lasts for 10 (6-hour) days divided into two sections. The supervised clinical work starts after this section is completed. Altogether, the training period lasts about 2.5 years	The educational course lasts for 10 (6-hour) days divided into two sections. The supervised clinical work starts after this section is completed. Altogether, the training period lasts about 2.5 years	Clinicians are supervised every 3 to 4 weeks for about 1½ years. Thereafter, approximately every 6 to 8 weeks for the last half year of training
Implementation outcome(s) affected	Fidelity, sustainability	Fidelity, sustainability	Acceptability, appropriateness, fidelity, and sustainability	Fidelity	Fidelity
Justification	Manualized treatment makes it easier to train therapists to a certain level of competence, as well as ensuring fidelity to the intervention (Wilson, 1996)	The educational materials are given to all of the clinicians in training to make sure everyone has the materials they need, when they need it, which facilitates training	Research suggest that effective training consist of presenting information or knowledge, providing demonstrations either live or recorded, combined with practicing key skills in training setting (Joyce and Showers, 2002)	Training is more effective when the information delivery methods are varied to cater to different learning styles, and clinicians are able to practice their skills in work settings (Joyce and Showers, 2002)	Most skills can be introduced in the educational courses, but they need to practice at work with proper supervision to become successful therapists (ie, Fixsen and Blase, 2009; de Vries and Manfred, 2005; Joyce and Showers, 2002)

^aNIMH: Network for Infant Mental Health.^bCOS-VF: Circle of Security-Virginia Family.

Table 3. Specifications of strategies used in the implementation of the Circle of Security-Virginia Family model in health care services.

Strategy	Create or change credentialing and licensure standards	Organize clinician implementation meetings	Obtain formal commitments	Mandate change	Centralize technical assistance
Actor(s)	Developers (United States) and supervisors	Supervisors	Clinicians who take part in the COS-VF ^a model training	Providers (NIHM ^b)	NIMH's technical support worker
Action	The therapist under training needs to be able to successfully code 80% of a set of 20 SSP ^c videos of caregiver-child dyads to become certified in coding attachment patterns using the SBSH-CS ^d . They also have to demonstrate competence while completing two cases under close supervision to become certified COS-VF therapists	Maintenance seminars are held at NIMH to provide the therapists an opportunity to discuss their experiences working with the COS-VF intervention and review videos of caregiver-child dyads to practice and maintain their skills	Clinicians have to obtain written commitments from their leaders that confirms that they are allowed to use 20% of their work hours on the COS-VF training	It is mandated that the clinicians in training have a SSP room available at their place of employment	Distributes educational information and materials online. Helps with technical support in issues related to COS-VF
Target action	Clinicians in training	Therapists	Leader(s) at the clinicians place of employment	Clinicians in training and their leaders	Therapists and clinicians in training
Temporality	Once during the educational course	One day each year	Before training	From the time they start working with case or families under supervision	Ongoing
Dose	There is no time frame for how long they have to complete the coding, or how many chances they get to succeed	6 hours	20% of their work hours on COS-VF training for the next 2.5 years	Ongoing	Ongoing or when needed
Implementation outcome(s) affected	Fidelity	Sustainability	Feasibility, penetration, and sustainability	Feasibility, appropriateness, and penetration	Acceptability, appropriateness, fidelity, and sustainability
Justification	This implementation strategy assures that the therapists have a certain competency level before they are allowed to treat patients and facilitates both fidelity to the intervention and evaluation of treatment results	Giving the therapist a chance to discuss their experiences and practice their skills facilitates fidelity and sustainability	Obtaining formal commitments ensure that both the clinicians who want to start COS-VF training and the leaders at their job are informed about what is expected of them and commit to doing so	The SSP room is a vital tool in evaluating the child's attachment patterns, as well as an important part of the therapist assessment and treatment plan (Ainsworth, 1978)	Access to educational information and materials, as well as the technical support needed while in training makes it easier to complete the training and to implement the intervention

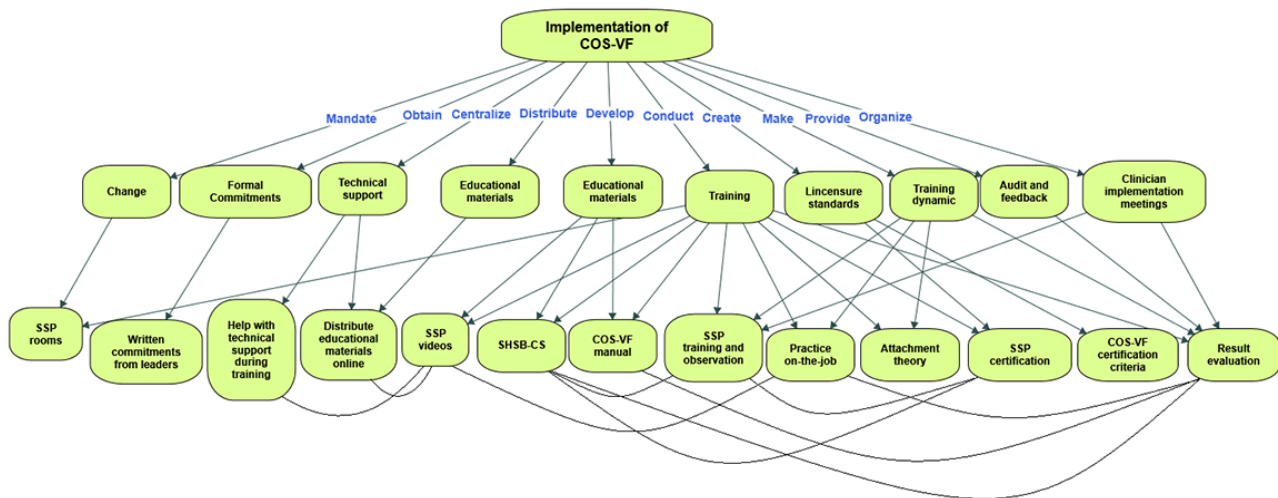
^aCOS-VF: Circle of Security-Virginia Family.

^bNIHM: Network for Infant Mental Health.

^cSSP: Strange Situation Procedure.

^dSBSH-CS: Secure Base-Safe Haven coding system.

Figure 2. A concept diagram of the implementation strategies and their interrelationships. COS-VF: Circle of Security-Virginia Family; SBSH-CS: Secure Base-Safe Haven coding system; SSP: Strange Situation Procedure.



Conduct Ongoing Training

The target group for COS-VF training are infant mental health practitioners who work within child welfare services, foster care, and child mental health. Clinicians who apply for COS-VF training are obligated to have at least 3 years of college or university education within health and social sciences, supplementary clinical education, and clinical practice. The educational training contains two sections consisting of 5 days each, with certification criteria for each part: (1) the SBSH-CS and (2) the COS-VF intervention. Curriculum for section one is attachment theory and caregiver-child interaction, following 4 to 5 months of practicing coding videotapes of families in the SSP. The second section involves learning core elements and each step in the COS-VF intervention according to the manual. After these two sections are completed, clinicians start working under regular supervision on the job. The duration of training and supervision depends on the families the clinicians have in therapy (ie, on how long the therapist deems it necessary for the family to gain new understanding of how to meet and support their child's needs according to attachment theory and change their parental behavior accordingly). It usually takes 2 to 2½ years from the start of training until clinicians become certified COS-VF therapists. The location of the training rotates between different regions of Norway for each new class to facilitate implementation of the intervention at the national level. This is part of the overall dissemination strategy where each strategy presented herein is implemented at each training site.

Make Training Dynamic

Training is made dynamic by using different methods of information delivery that cater to different learning styles by (1) Providing new skills through lectures, (2) Group work, (3) Watching videos of caregiver-child dyads with different attachment issues, as well as (4) Having to practice coding videos to a certain competence level before they can (5) Start working with families under supervision (see Table 2 and Figure 2).

Audit and Feedback

Clinicians in training must work on two families under supervision before they can become certified COS-VF therapists. Clinicians are divided into groups of four and receive supervision in a group setting either through Skype or face-to-face. Supervision is based on the principles of auditing and feedback where therapists and supervisors jointly watch and examine video recordings of therapists' sessions with families. During supervision, there should be active reflection between the clinician and the supervisor, as well as effective engagement in a reflective dialogue concerning the clinician's strengths and abilities around the circle when working with the caregivers. The underlying framework is the one of the "nested hands." The supervisor is the "hands" to the therapist, the therapist the "hands" to the caregiver, and the caregiver the "hands" to the child (ie, the hands holding the child or caregiver or therapist in his or her experiences with casework or parenting around the circle).

In COS-VF, clinicians are supervised every 3 to 4 weeks for about 1½ years and then with reduced supervision approximately every 6 to 8 weeks for the last half year. During the first family intervention, supervisors have the primary role in implementing the intervention in cooperation with the clinicians in training, whereas the clinician takes the primary role with the second family. After certification, therapists no longer receive any formal supervision from the COS-VF providers (NIMH), but they can take part in maintenance seminars that NIMH organizes once a year (see Clinician Implementation Meetings below).

Create or Change Credentialing and Licensure Standards

COS-VF therapists under training must become certified in both (1) Coding attachment patterns of caregiver-child dyads using the SSP and (2) The intervention. As part of their training course, they learn to use the SBSH-CS and must successfully code 16 (ie, 80%) out of 20 SSP videos to become certified. They must pass the course before they can receive their certificate. Therapists in training are never told how many mistakes they had if they fail. They are simply given general

feedback on whether they were close or far from passing to ensure the answers are never disclosed and increase the likelihood of passing the course by demonstrating competence rather than because of any nonspecific factors (eg, chance or poor course design).

To become certified COS-VF therapists, clinicians in training have to demonstrate competence in each of the following areas (each with a separate set of criteria): (1) assessment and treatment planning (eg, finding parents' linchpins to choose appropriate video clips for treatment to demonstrate underutilized strengths), (2) therapist-parent interaction (eg, how the therapist is the "nested hands" for parents), and (c) therapist-supervisor interaction (eg, engaging in reflective dialogue with a supervisor). Certification is based on a joint reflective dialogue between the supervisor and therapist to allow judgments on whether the therapist is sufficiently competent to conduct the intervention without supervision.

Organize Clinician Implementation Meetings

Every year, the program providers (NIMH) invite COS-VF therapists to a maintenance seminar, where they discuss their experiences. These seminars allow the therapists to train and maintain their skills, as well as provides a forum for discussing their COS-VF-related experiences with other therapists. The health care services (ie, therapists' workplace) must cover a small seminar fee, travel costs, overnight stays, and other expenses related to the seminar.

Obtain Formal Commitments

Clinicians who apply for COS-VF training must commit to using at least 10% to 20% of their work hours on COS-VF. To ensure this, they have to obtain a written consent by their immediate supervisor or leader at their workplace. This makes the likelihood of misunderstandings between leaders and their employees about the requirements of the training less probable, as well as making it easier for clinicians to spend the time they need on their training.

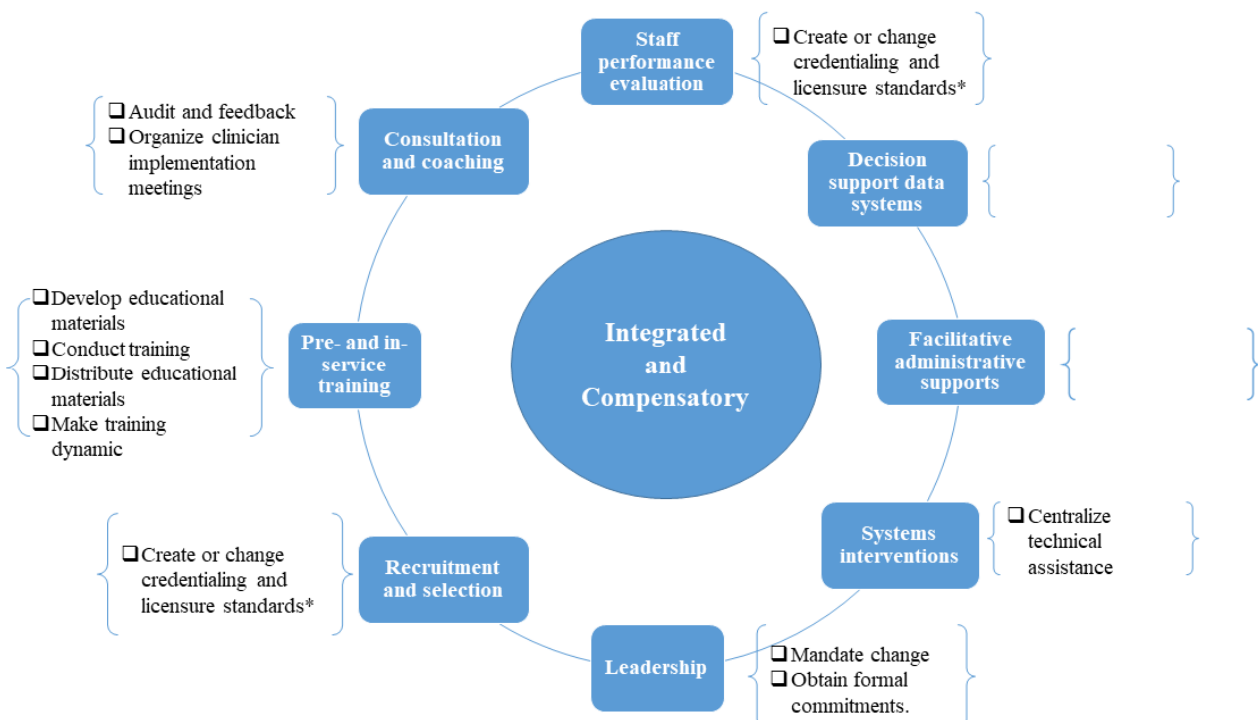
Mandate Change

To take part in COS-VF training, it is mandated that clinicians have access to an appropriate room for conducting the SSP (eg, video cameras and two-way mirror), or else they would not be able to carry out the intervention with families, which is part of the training. It also ensures intervention fidelity after certification, as SSP observations are part of the assessments that should be routinely conducted with each family before and after the intervention.

Centralize Technical Assistance

There are personnel at NIMH in charge of distributing all the information concerning COS-VF (ie, course information, educational materials, SSP training videos, etc), as well as technical support for clinicians in training (see Figure 2 and Table 3); an implementation strategy that makes sure they have easy access to everything they need throughout training, which makes it easier for them to succeed.

Figure 3. Display of the implementation strategies placed within the core implementation components. COS-VF: Circle of Security-Virginia Family. Asterisk (*): Create or change credentialing and licensure standards is mentioned twice in the digram as the strategy involves aspects which apply to both recruitment and staff performance evaluation.



Core Implementation Components

As the COS-VF providers were inspired by Fixsen and Blasé's [14] core implementation components, we found it interesting to visualize which of the components were in place and which of the components needed more attention. This was done by organizing the strategies within their diagram of core implementation components. As depicted in Figure 3, pre- and in-service training has gotten a lot of focus in the implementation of COS-VF. There are also some strategies involved with systems interventions, recruitment and selection, consultation and coaching, as well as staff performance evaluation. We also added our own component and named it leadership, a component that has been taken into consideration during the implementation of COS-VF. Facilitative administration and decision support data system, however, do not have any strategies at this point.

Discussion

Principal Findings

The aim of this study was to provide a systematic and comprehensive review of strategies involved in the implementation of the COS-VF model in Norway. By combining informal interviews and documentation from COS-VF providers (ie, NIMH), 10 strategies were identified based on the ERIC taxonomy [7]: (1) develop educational materials, (2) distribute educational materials, (3) conduct ongoing training, (4) make training dynamic, (5) auditing and feedback, (6) create or change credentialing and licensure standards, (7) organize clinician implementation team meetings, (8) obtain formal commitments, (9) mandate change, and (10) centralize technical assistance.

Before COS-VF was implemented in Norway, different educational materials were developed and available (ie, SBSH-CS, SSP videos, and the COS-VF manual). Research suggests that manualized therapies make it easier to train therapists to a certain competency level, easier for supervisors to monitor trainees' abilities, and facilitate future research. Previous research also suggests that manualized treatments increase intervention fidelity [28]. However, it is important to note that fidelity is more than just adherence to a set of well-defined procedures outlined in a manual but also includes competence in the delivery of an intervention and patient engagement, among other things [30]. Manuals solely provide a minimum operational description of how therapists are expected to behave and what they are expected to provide their patients [31]. Thus, it is important to consider who will be using these manuals, where, and what training is necessary for their effective use in practice.

When selecting and recruiting from applicants who want to take part in COS-VF training, there are several factors that need to be taken into consideration such as previous education, work experience, and current place of employment, that is, whether they are within the target group have access to families and mandate to conduct long-term therapy. However, it is still unknown what experience and credentials should be required when selecting staff for manual-based interventions to achieve effective use of treatment manuals [28], or which health care services have the organizational capacity to implement new

practices [32]. Because staff and service selection are largely neglected areas within implementation research, it is difficult to give any clear directions regarding maintenance or improvement issues related to this area of the COS-VF implementation process [24]. Thus, it is crucial to conduct more research on staff and health care service selection, as these are important variables in promoting successful implementation.

Training in COS-VF is designed in a way that provides knowledge of theory, introduces components and rationale for key practice, provides opportunities to practice new skills, and receive feedback in a safe training environment (ie, ongoing, dynamic training, auditing, and feedback). This is consistent with research that learning a new intervention requires significant behavior change for therapists, as well as process guidance [33]; ie, close supervision, emotional support, result evaluation, and feedback based on practical experience. This is supported by Joyce and Showers' [34] meta-analysis that shows that real learning and implementation occurs on the job, with supervision. Such on-the-job training, eventually, culminates in certification as COS-VF therapists (ie, created credentialing and licensure standards) and a level of competency, which suggests that graduates can deliver COS-VF without supervision. However, although training and supervision in COS-VF is well-attended to, it is an open question whether continued supervision should be provided after therapists finish their formal training to a greater degree than what is currently offered (ie, voluntary annual maintenance seminars). As Fixsen and colleagues [21] have pointed out, training and supervision are one of the principal ways in which behavior change is brought about not only at the start of the implementation but also throughout the lifespan of an intervention.

An implementation protocol can help implementation of an intervention, is useful, and contributes to the understanding of subsequent research, regardless of the intervention's evidence base. Furthermore, one of the greatest advantages of developing an intervention protocol for COS-VF is that it facilitates transferability because the replication of an intervention is highly dependent on the conditions of the implementation (ie, whether or not the providers followed a protocol: [35]). Implementation fidelity will make it easier to replicate findings from research on the intervention when or if the implementation expands nationally and internationally, which again will ensure the generalizability of the results.

Future Development

COS-VF therapists receive supervision during training; however, there is no evaluation of their work after they become certified. That is not to say that they do not receive evaluation by their employers; however, this is not a strategy that is part of the COS-VF implementation. The intention of staff evaluation is to assess the use and outcomes of skills therapists are taught in training and help them continue to improve their effectiveness with patients [21,36,37]. Evaluating therapist performance and using fidelity measures provides useful feedback concerning implementation efforts, training, and supervision. Furthermore, as previous research suggests that high fidelity implementation produces better outcomes for its recipients (ie, the patients; eg, [38]), this could be an area for quality development.

Previous research (ie, [21,39]) proposes that frequent process and outcome reports guide decision making at the policy- and practice-level of organizations, as well as making it easier for organizations to continuously improve. However, there were no strategies involved in assessing key aspects of overall performance in COS-VF. This area should thus also receive more attention in further quality development of COS-VF. Furthermore, COS-VF has no strategies involved with administrative support; ie, components that give attention to policies, procedures, structures, culture, and climate, to assure alignment of these areas of an organization with the needs of the therapists. Previous research suggests that this is an important part of the implementation process that should not be disregarded [21,40] and could serve as an area for intermediary organizations such as the NIMH at the Regional Centre for Child and Adolescent Mental Health, to support health and clinical services.

Limitations

A key limitation with this implementation protocol is that it was developed in a post-hoc manner, rather than during the planning stage of implementation. However, developing the implementation protocol as part of a reflective or evaluation phase allowed us to identify and critically appraise key aspects of the implementation process. This may point toward weaknesses in the implementation of COS-VF, which, in turn, makes it possible to identify areas in need of further improvement. In a sense, this may be one of the strengths of developing implementation protocols post-hoc and highlights why it is better to design such implementation protocols after the deployment of an intervention, rather than never. This implementation protocol shows that the competency area of the implementation of COS-VF is taken care of to a considerable extent, whereas the implementation of COS-VF in areas of organization and leadership is more limited and less developed.

Implementation protocols are constrained to local and contextual conditions under which a given intervention is implemented (even though this may be at a national or international level). Therefore, one should be careful in considering the potential usefulness of the outcomes of this study to other interventions or countries. However, although delimited to a specified intervention or context, implementation protocols may be the “missing link” necessary to replicate studies and to transfer theory and research into practice.

The third limitation involves the ERIC taxonomy [7] and the fact that the expert panel that participated in developing the taxonomy consisted mostly of implementation and clinical experts from the United States. It is possible that some strategies are more applicable in North-American settings and less applicable outside of North America. It may even be that there are unidentified strategies that are applicable outside American settings that are currently not included in the taxonomy. This could have affected the conceptualization of implementation strategies in this study. Nevertheless, to the best of our knowledge, there is no evidence that suggests that the compilation is not applicable across different contexts.

Conclusions

This study describes the development of a post-hoc implementation protocol for the implementation of COS-VF in Norwegian health and clinical services. The development of the implementation protocol has made it possible to further develop and quality improve the implementation of COS-VF. Although COS-VF has yet to be evaluated, the identified implementation strategies may provide a valuable contribution to the understanding of subsequent research findings and blueprint for future implementation of COS-VF and, if possible, other interventions and in other countries as well. The implementation protocol will also make it easier for future research to replicate research findings and avoid “type III” errors.

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Conflicts of Interest

KS and FD work at the research unit at the NIMH but have no responsibilities in the training or implementation related to COS-VF.

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Abbreviations

- AIF:** Active Implementation Framework
COS-VF: Circle of Security-Virginia Family
ERIC: Expert Recommendations for Implementing Change
NIMH: National Network for Infant Mental Health
SBSH-CS: Secure Base-Safe Haven coding system
SSP: Strange Situation Procedure

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