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Protocol

Effects of Deep Versus Moderate Neuromuscular Blockade in Laparoscopic Gynecologic Surgery on Postoperative Pain and Surgical Conditions: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postoperative pain, especially shoulder pain, is commonly reported after laparoscopic gynecologic procedures. Some studies suggest that a lower insufflation pressure may reduce the risk of postoperative pain; however, there is no agreement on the optimal pneumoperitoneum pressure during gynecologic laparoscopic surgery or whether lower pressure would lead to clinically significant improvements without increasing operative complications. Questions remain regarding the clinical significance of improvements, safety, and cost-effectiveness of deep neuromuscular blockade with low-pressure pneumoperitoneum.

Objective: The primary objective of this study was to assess the superiority of anesthesia with deep neuromuscular blockade with pneumoperitoneum 8 mm Hg over moderate blockade with pneumoperitoneum 12 mm Hg in terms of overall pain 24 hours after surgery in adult women undergoing pelvic surgery for hysterectomy or benign adnexal diseases. Effects on the intensity and timing of postoperative pain in specific locations, surgeon satisfaction, respiratory and hemodynamic stability, operating times, and direct and indirect costs will be assessed.

Methods: In this multicenter, randomized controlled trial with a superiority design, 300 patients will be randomly allocated in the ratio 1:1 to moderate neuromuscular blockade with a target insufflation pressure of 12 mm Hg or deep neuromuscular blockade with a target insufflation pressure of 8 mm Hg, with stratification by type of surgery and clinical center. The patient, the statistician, and the nurse who will assess the primary endpoint will be blinded to the allocation.

Results: Recruitment to this trial is expected to open in June 2018 and is expected to close in June 2019.

Conclusions: This study is designed to confirm the reported benefits of postoperative pain and provide additional data needed to address questions regarding the effects of this intervention on operating theater management and direct and indirect costs. Strengths of this protocol include the large sample size distributed among diverse institutions across the Italian territory and the

collection and analysis of data on numerous secondary objectives. Limitations include the possible introduction of bias because the surgeon and anesthesiologist are not blinded to the intervention.

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KEYWORDS

clinical trial; laparoscopic surgery; anaesthesia; neuromuscular blockade

Introduction

Postoperative pain, especially shoulder pain, is commonly reported after laparoscopic gynecologic procedures [1]. Some studies have suggested that using a lower insufflation pressure may reduce the risk of postoperative pain [2]; however, there is no agreement on the optimal pneumoperitoneum pressure during gynecologic laparoscopic surgery or whether lower pressure would lead to clinically significant improvements without increasing operative complications. In a study of 100 laparoscopic cholecystectomy procedures randomly allocated to low-pressure pneumoperitoneum (8 mm Hg) or normal pressure (14 mm Hg), low pressure significantly decreased the frequency and intensity of postoperative shoulder pain, analgesics consumption, and length of hospital stay [2].

In gynecologic procedures, a study of 150 patients undergoing gynecologic laparoscopy randomly allocated to abdominal insufflation pressures of 8 mm Hg (n=54), 12 mm Hg (n=45), or 15 mm Hg (n=51), the pain scores were found to be significantly better with low insufflation pressure; however, there was a trend toward longer operation times and increased hemorrhage in this group [3]. A recent systematic review did not confirm this reported increase in operating time or blood loss with lower pressure; however, it did raise questions regarding whether the benefit of the observed reduction in postoperative pain could offset the decrease in the quality of surgical conditions [4]. The authors reported an association between lower pressure and increased risk of poorer surgical field visibility (relative risk 10.31; 95% CI 1.29-82.38).

Thus, there appears to be a consensus that low insufflation pressures can reduce postoperative pain [5-9], and this would appear to suggest a way to improve surgical conditions at lower insufflation pressures. For this purpose, it has been suggested that neuromuscular blockade (NMB) may help to maintain a sufficient intra-abdominal workspace at lower insufflation pressure [10]. NMB induces dose-dependent muscle relaxation that allows the muscles to stretch to their maximum length [11]. This may improve the surgical working space during laparoscopic procedures.

The advantages of deep NMB in laparoscopic surgery are not well established. Several studies have examined the effect of deep NMB on the working surgical space and the relationship between relaxation and insufflation pressure in nongynecologic [12-14] and gynecologic procedures [15,16]. The use of deep NMB compared with moderate NMB maintained during surgery is associated with improved surgical conditions during laparoscopic procedures (reviewed in [17]). NMB also improved surgical conditions when suturing the abdominal fascia [18]. A

randomized controlled trial comparing deep NMB with 8 mm Hg pneumoperitoneum with moderate NMB with 12 mm Hg pneumoperitoneum in laparoscopic hysterectomy revealed a reduction in postoperative shoulder pain, with no differences in duration of surgery, length of hospital stay, or time to recovery of daily activities [19]. Thus, questions remain regarding the clinical significance of improvements, safety, and cost-effectiveness of deep NMB with low-pressure pneumoperitoneum.

Economic efficiency should not be considered reductively, in terms of mere cost savings, but in its most correct sense by determining the best anesthetic conditions for the patient and the surgeon and by identifying the best relationship between efficacy, safety, and cost-effectiveness in the use of health resources [20]. Optimal management of anesthesia, including the type of NMB, can facilitate the conduction of surgery and have positive effects on peri- and postoperative outcomes. New NMB agents and their antagonists allow precise control of awakening times for efficient operating room scheduling, avoiding cost increases because of personnel overtime. For example, rapid recovery may prevent some of the frequent and numerous side effects associated with longer sedation and the associated increases in hospital cost [21].

The availability of neuromuscular monitoring and agents to reverse the effects of nondepolarizing muscle relaxants has made the use of deep NMB safer and more practical. Reversal agents work either by increasing acetylcholine levels through competitive inhibition of acetylcholinesterase (neostigmine) or by encapsulating aminosteroid NMB agents (sugammadex) [22]. Neostigmine is associated with a higher risk of postoperative residual curarization, compared with sugammadex [23,24]. Sugammadex rapidly forms an essentially irreversible dose-dependent chelating complex with rocuronium and other aminosteroid muscle relaxants [25]. This allows reversal of all levels of NMB with complete recovery of muscle function almost immediately after administration.

The purpose of this study was to investigate whether deep NMB with reduced pressure pneumoperitoneum is superior to moderate NMB with normal pressure pneumoperitoneum, in terms of overall pain 24 hours after waking in patients undergoing gynecologic laparoscopic procedures. In addition, the effects on the intensity and timing of postoperative pain in specific locations, surgeon satisfaction, respiratory and hemodynamic stability, operating times, and direct and indirect costs will be assessed.

Methods

Study Objectives

The primary objective of this study was to assess the superiority of anesthesia with deep NMB with pneumoperitoneum 8 mm Hg over moderate blockade with pneumoperitoneum 12 mm Hg, in terms of overall pain 24 hours after waking in adult women undergoing pelvic surgery for hysterectomy or benign adnexal diseases.

Secondary objectives will be to assess differences between the 2 groups in terms of:

- Patient relaxation quality during surgery
- Need for administration of additional NMB agents based on intraoperative train-of-four (TOF)
- Surgeon satisfaction (Likert scale: 1=impossible to proceed, 2=insufficient, 3=sufficient, 4=good, and 5=excellent) on each of the following:
 - neck strain
 - back strain
 - visual acuity
 - overall satisfaction
- Hemodynamic stability during surgery, determined clinically by monitoring systolic and diastolic blood pressures, electrocardiogram and, in part, by capnography.
- Respiratory stability during surgery, determined clinically by monitoring ventilation parameters: O₂ saturation, end-tidal CO₂, and CO₂ insufflation pressure; tidal volume; positive end-expiratory pressure; inspiratory-to-expiratory ratio; fractional O₂ percentage; and blood gases.
- Direct and indirect costs
- Duration of surgery (from first access to umbilical closure, in minutes)
- Time to awakening (from induction to awakening, in minutes)
- Time from the end of the surgery to awakening (modified Wilson sedation scale)
- Time to discharge from postanesthesia care unit (PACU; from induction to discharge, in minutes)
- Time in operating theater stay from entry to discharge to PACU or ward
- Postoperative nausea and vomiting (PONV), at the same time points as for pain, using a 0 to 10 numerical rating scale (NRS)
- Time to discharge, evaluated with the Postanaesthetic Discharge Scoring System [26]

Trial Design

This will be a multicenter, randomized controlled trial with a superiority design. Patients will be randomly allocated in the ratio 1:1 to one of two parallel groups with stratification by type of surgery and clinical center.

Eligibility Criteria for Participants

Eligible women scheduled for an elective laparoscopic or robotic gynecologic procedure with an expected duration <90 min performed under general anesthesia and requiring tracheal

intubation (eg, cystectomy, hysterectomy, salpingo-oophorectomy) will need to satisfy the following criteria:

- Age 18-60 years
- Body mass index between 20 and 30 kg/m²
- American Society of Anesthesiologists class 1 or 2
- Able to provide informed consent to trial procedures (eg, no speech or hearing impairment or language barriers)

Patients meeting any of the following criteria will be excluded:

- Pregnancy
- Surgery for endometriosis, diagnostic laparoscopy with chromosalpingoscopy, myomectomy, or tube ligation
- Anticipated airway difficulty
- Requirement for rapid sequence induction
- Anticipated intensive care unit admission or when extubation is not planned
- Hepatic or renal failure
- Baseline heart rate <50 bpm
- Documented or suspected neuromuscular disorders, Guillain-Barré syndrome, cerebrovascular accidents with residual neurologic deficits, Parkinson disease, and myasthenia gravis
- Patients receiving fusidic acid or toremifene 24 hours before surgery and hormonal contraceptives
- Patients receiving drugs for or affected by medical conditions that may prolong or shorten the duration of rocuronium effect (eg, aminoglycosides, magnesium)
- Patients with a history of allergy to rocuronium, neostigmine, or sugammadex
- Any condition making the administration of patient satisfaction questionnaire difficult or impossible.

Setting and Data Collection Locations

Participating centers will be selected among those where laparoscopic and/or robotic gynecologic surgery is standard of care, performing at least 100 laparoscopic hysterectomies per year (or 200 laparoscopic procedures per year), with sampling distributed geographically across Italy. Both university and general hospitals can participate. At each center, a single surgeon (and team) and a single anesthesiologist (and team) will be involved.

Intervention/Treatment

Preparation for Surgery and Induction of Anesthesia

All patients will undergo intestinal preparation on the day preceding surgery and antibiotic prophylaxis (according to local hospital guidelines) 30 min before skin incision.

Premedication, for example, with midazolam 0.04 mg/kg, desametasone 0.1 mg/kg, and H₂ antagonists will be performed before anesthesia induction in reception (actual drugs will be selected by the anesthesiologist).

Intraoperative monitoring will include electrocardiography, noninvasive arterial pressure measurements, nasogastric tube placement, and pulse oximetry. In addition, acceleromyography (using a dedicated instrument) will be used to monitor the response of the adductor pollicis muscle. Neuromuscular

monitoring and management will follow Good Clinical Research Practice guidelines.

Anesthesia will be induced with propofol 2-2.5 mg/kg, remifentanyl 0.1 µg/kg/min, and desflurane 4% as standard dosages, using target-controlled infusers.

Before rocuronium administration, the acceleromyography instrument will be calibrated and stabilized; a 50-Hz tetanic stimulation will be applied for 5 s, the acceleromyography instrument will be calibrated, and a series of TOF measurements will be documented for >2 min until a stable baseline is obtained (<5% variation in the TOF ratios).

Trendelenburg position will be maintained as required for surgery.

Analgesic transition will be achieved with fentanyl 100 µg at induction. Starting 20 min before the end of surgery, postoperative analgesia will be ketorolac 90 mg/24 hours in continuous infusion.

Group A (Intervention): Deep Neuromuscular Blockade

Patients in group A will undergo anesthesia with deep NMB attained during surgery using rocuronium 0.6 mg/kg, followed by orotracheal intubation within 60 s to 120 s after confirmation of relaxation and intra-abdominal CO₂ insufflation to a pressure of 8 mm Hg.

Anesthesia will be maintained with target-controlled infusion of propofol and remifentanyl while monitoring the bispectral index (A-2000 BIS monitor; Aspect Medical Systems, Inc, Natick, MA, USA). After induction, rocuronium will be continuously infused and titrated to maintain the posttetanic count (PTC) at 1 to 2 throughout surgery. NMB will be reversed at the end of surgery with sugammadex 4 mg/kg at PTC of 1 or 2.

Group B (Control): Moderate Neuromuscular Blockade

Patients in group B will undergo anesthesia with moderate NMB with rocuronium bromide 0.6 mg/kg, followed by orotracheal intubation within 60 s to 120 s after confirmation of relaxation and intra-abdominal CO₂ insufflation pressure of 12 mm Hg.

Anesthesia will be maintained with target-controlled infusion of propofol and remifentanyl while monitoring the bispectral index (A-2000 BIS monitor; Aspect Medical Systems Inc). After induction, rocuronium will be continuously infused and titrated to maintain TOF response at 1-2 throughout surgery. NMB will be reversed at the end of surgery with sugammadex 2 mg/kg.

Insufflation Pressure

The target insufflation pressure will be different in the 2 groups. However, the intraperitoneal pressure will be adjusted to the lowest pressure necessary to maintain the surgical field. The lowest stable (ie, preserving a viable surgical field) intraperitoneal pressure reached during surgery will be recorded.

Reversal and Predischarge Procedures (Including Postoperative Nausea and Vomiting Prophylaxis)

Patients in group A will have NMB reversed with intravenous sugammadex at 4 mg/kg at PTC of 1 or 2 and those in group B with sugammadex 2 mg/kg at a TOF count of 1 or 2. The time from administration of the reversal agents to a TOF ratio of 0.9 will be recorded (time to reversal).

Analgesic transition will be continued (as described previously). PONV prophylaxis will be achieved with coinfusion of 8 mg intravenous ondansetron+100 mg intravenous ranitidine, and the patient will be awakened in the operating theater.

Table 1 provides a comparison between intervention and control groups.

Table 1. Comparison of intervention and control groups.

Intervention	Group A (intervention): deep neuromuscular blockade	Group B (control): moderate neuromuscular blockade
Type of NMB ^a	Deep	Moderate
Drug	Rocuronium bromure 0.6 mg/kg	Rocuronium bromure 0.6 mg/kg at induction
Orotacheal intubation	Within 60-120 s	Within 60-120 s
Intra-abdominal insufflations	8 mm Hg	12 mm Hg
NMB maintenance	Target-controlled infusion of propofol and remifentanyl while monitoring the bispectral index; rocuronium will be continuously infused and titrated to maintain the PTC ^b at 1-2 throughout surgery	Target-controlled infusion of propofol and remifentanyl while monitoring the bispectral index; rocuronium will be continuously infused and titrated to maintain TOF ^c response at 1-2 throughout surgery
NMB reversal	Sugammadex 4 mg/kg at PTC of 1 or 2	Sugammadex 2 mg/kg

^aNMB: neuromuscular blockade.

^bPTC: posttetanic count.

^cTOF: train-of-four.

Table 2. Secondary outcomes.

Outcome	Definition/variable	Measurement
Pain	Rescue dose needed, yes/no	Determined clinically
Pain	Rescue doses in the first 24 and 48 hours, n	Determined clinically
Pain	AUC ^a of NRS ^b at specific sites: intrascapular, incisional, lower abdomen	NRS at predefined time points plus at rescue dose request
Pain	Maximum pain, Time to maximum pain, Time to pain <4	NRS at predefined time points plus at rescue dose request
Patient movement	Any patient movement	Reported by the surgeon or anesthesiologist
Patient movement requiring re-curarization during surgery	Any patient movement	Reported by the surgeon or anesthesiologist
Surgeon satisfaction	Likert scale 1-5; neck strain, back strain, visual acuity, overall satisfaction	Questionnaire: every 15 min from first laparoscopic view until removal of laparoscopes at the end of surgery or up to 8 hours from the first score.
Hemodynamic stability during surgery	Yes/no	Determined clinically: systolic and diastolic blood pressures, total diuresis, need for catecholamines, etc
Respiratory stability during surgery	Yes/no	Determined clinically by monitoring PaO ₂ , PaCO ₂ , etc
Duration of surgery from first access to umbilical incision closure	Measured in minutes	N/A ^c
Time from administration of NMB ^d antagonist to awakening	Measured in minutes	N/A
PONV ^e	AUC of NRS 0-10 in the first 24 hours	N/A
Time from surgery to discharge	Measured in days	Postanesthesia Discharge Scoring: ≥2 assessments > 8.5 hours apart
Postoperative evaluation	Composite endpoint	Telephone questionnaire [26]
Direct costs	Number, description, and type of drug; type of intervention (International Classification of Diseases, Ninth Revision, ICD9 code); year; operating theater time; NMB reversal time (end of surgery to extubation); type and number of personnel present; anesthesia; presence/absence of postoperative residual curarization (PORC); prophylactic therapy for PORC; rescue therapy for PORC; PACU ^f stay, yes/no; PACU stay duration, minutes; PACU stay >60 min, yes/no; intensive care unit admission, yes/no; with immediate extubation?, with early extubation?, with delayed extubation?	These data will be registered on a dedicated monitoring form for each patient.
Indirect costs	Absence from work; lost productivity; QoL ^g	EuroQoL-5 dimensions questionnaire (possibly other appropriate instruments)

^aAUC: area under the curve.

^bNRS: numerical rating scale.

^cN/A: not applicable.

^dNMB: neuromuscular blockade.

^ePONV: postoperative nausea and vomiting.

^fPACU: postanesthesia care unit.

^gQoL: quality of life.

Outcome Measurements

Primary Outcome

The primary outcome will be the area under the curve (AUC) of overall pain in the first 24 hours after surgery, assessed on an NRS of 0 to 10 administered by a nurse blinded to study group allocation.

AUC for overall pain will be calculated on the NRS measurements at predetermined time points (30 min, 60 min, 120 min, 4 hours, 8 hours, 12 hours, and 24 hours) plus any time when rescue analgesic is requested.

Secondary Outcomes

Secondary outcomes are summarized in [Table 2](#).

Procedures lasting >90 min from first access to umbilical incision closure will be excluded from the analysis. The surgeon will rate surgical conditions every 10 min during the procedure and again at the end, using a 5-point scale (1=excellent, 2=good, 3=acceptable, 4=poor, and 5=inadequate).

In the economic analysis, direct costs will be based on operating and patient recovery times in the context of each hospital center, including time in the operating room and PACU and costs for the professionals monitoring the patient before extubation and resumption of spontaneous respiration. Indirect costs will be captured with the EuroQOL-5 dimensions quality of life questionnaire, lost productivity, and absence from work.

Sample Size Calculation

A sample size determination was conducted for the main outcome variable. Hypothesizing an AUC for overall pain in the first 24 hours of 144 patients in group B and 120 patients in group A, a common SD of 60, 140 patients per group will be necessary to achieve 92% power with an alpha error of 5% with a 2-sided *t* test for independent samples.

On the basis of preliminary results of a pilot study conducted at the Catania center, we expect to lose no more than 5% of patients because of surgery durations >90 min; thus, we plan to enroll 300 patients to be allocated in the ratio 1:1 in 2 groups.

Interim Analysis

No interim analysis is planned.

Randomization: Sequence Generation, Allocation Concealment Mechanism, and Implementation

Sequence Generation

Allocation sequence to groups A and B will be obtained using the “ralloc” module in Stata 14 (StataCorp LLC, College Station, Texas), with blocks of variable size (4-6-8), and stratified by participating center and type of surgery (hysterectomy). The algorithm for sequence generation will be maintained by the study statistician and will not be communicated to any additional study staff.

Allocation Concealment Mechanism

The study statistician will prepare the appropriate number of numbered, opaque, sealed envelopes for each center. These will be maintained at each center by an appropriately trained research nurse. At the time of anesthesia induction, the surgical nurse will open the relevant envelope, and the anesthesiologist will proceed to the allocated treatment.

Data Collection and Management

Study data on the primary and secondary outcomes will be collected from clinical charts and by dedicated data personnel using Research Electronic Data Capture electronic data capture tools [27]. The electronic database will be built by bioinformatics experts and will include built-in quality checks for key variables.

Statistical Analysis

Statistical Methods for Analyzing Primary and Secondary Outcomes

The primary endpoint (AUC for pain) will be compared by Student *t* test. *P* value <.05 will be considered significant. Descriptive statistics will be obtained for all variables assessed in the study population. Mean and SD will be used for normally distributed variables, and mean and interquartile range will be used for skewed distributions and proportions for categorical variables. Whenever relevant, 95% CIs will be calculated.

For group comparisons, Student *t* test (rank-sum test or Mann-Whitney test for skewed distributions) will be used for quantitative variables (analysis of variance or Kruskal-Wallis for >2 groups, respectively) and Pearson chi-square test (Fisher exact test where appropriate) for categorical variables. Two-tailed tests will be used in all cases. *P* value <.05 will be considered significant.

Generalized mixed models will be used to assess differences between groups in endpoints measured at several time points.

A detailed statistical analysis plan will be developed after the first 40 patients have been enrolled.

Methods for Any Additional Analyses

The main analysis will be on the whole study population. Additional analyses will be stratified by type of intervention. Also, analyses will consider uterus volume as a proxy for complexity of surgery.

Blinding

Anesthesiologist and surgeon will be aware of the treatment assignment. The patient, the nurse who will assess the primary outcome (NRS on day 1), and the statistician will be blinded.

Ethical Issues

This protocol, patient information sheet, and patient consent form have been reviewed and approved by the local ethics committee of Udine. All participating centers will obtain approval from their local ethics committee before starting enrollment. Italian law requires that approval is obtained first from the ethical committee of the coordinating center before obtaining approval from the other participating centers. Any protocol modifications will be submitted for review by each ethical committee. The study has been registered at Udine Ethical Committee (registration number: 23445/Ceur—4/9/2017). Written informed consent will be obtained directly from each patient by the participating anesthesiologist at the presurgery visit. Italian law does not allow consent from health care surrogates.

Results

Recruitment to this trial is expected to open in June 2018 and is expected to close in June 2019.

Discussion

Laparoscopic surgery provides benefits that include less bleeding, faster recovery, and shorter hospital stays. However, it is performed in a restricted space that may limit the surgeon's view and range of motion. Higher CO₂ insufflation pressure provides more insufflation volume [28] and improves surgical field visibility [29] but is associated with increased postoperative side effects [1]. During laparoscopic procedures, maintaining deep NMB, compared with moderate NMB, is associated with improved surgical conditions, as reviewed in Madsen and colleagues' study [17]. NMB also improved surgical conditions when suturing the abdominal fascia [18]. However, the advantages of deep NMB in laparoscopic surgery are not well established, and questions remain regarding the clinical significance of the improvements, safety, and cost-effectiveness.

This study may confirm the reported benefits for postoperative pain and provide the additional data needed to address questions

regarding the effects of this intervention on operating theater management and direct and indirect costs.

Strengths of this protocol include the large sample size and the participants being distributed among diverse institutions across the Italian territory, which will increase the generalizability of the results. The study will provide a comprehensive picture of the effect of and the collection and analysis of data on numerous secondary objectives, including an analysis of direct and indirect costs, to determine the overall effect of the intervention. Limitations include the possible introduction of bias because the surgeon and anesthesiologist will not be blinded to the intervention. However, potential bias will be reduced through blinding of the nurse who will assess the primary outcome (ie, the AUC of overall pain during the first 24 hours after surgery measured on an NRS of 0-10). Moreover, the randomization sequence will be generated centrally and allocation concealed in opaque, sealed envelopes until the time of anesthesia induction.

Authors' Contributions

EDR, YL, LS, GLC, AC, PS, and EV developed the original study design. EDR, YL, LS, and GLC developed the research protocols. EDR, YL, EV, and LS performed the sample size calculation. EDR, YL, AC, PS, ACM, and EV are responsible for the clinical input. EDR, YL, LS, EV, and GLC drafted the manuscript. All the authors have approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

- AUC:** area under the curve
- NMB:** neuromuscular blockade
- NRS:** numerical rating scale
- PACU:** postanesthesia care unit
- PONV:** postoperative nausea and vomiting
- PTC:** posttetanic count
- TOF:** train-of-four

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Protocol

Reducing HIV Vulnerability Through a Multilevel Life Skills Intervention for Adolescent Men (The iREACH Project): Protocol for a Randomized Controlled Trial

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Abstract

Background: Few HIV interventions have demonstrated efficacy in reducing HIV risk among adolescent men who have sex with men (AMSM), and fewer still have recognized the unique needs of AMSM based on race/ethnicity or geographical setting. Recognizing that youths' HIV vulnerability is intricately tied to their development and social context, delivering life skills training during adolescence might delay the onset or reduce the consequences of risk factors for HIV acquisition and equip AMSM with the skills to navigate HIV prevention. This protocol describes the development and testing of iREACH, an online multilevel life skills intervention for AMSM.

Objective: This randomized controlled trial (RCT) aims to test the efficacy of an online-delivered life skills intervention, iREACH, on cognitive and behavioral HIV-related outcomes for AMSM.

Methods: iREACH is a prospective RCT of approximately 600 cisgender adolescent males aged 13 to 18 years who report same-sex attractions. The intervention will be tested with a racial/ethnically diverse sample ($\geq 50\%$ racial/ethnic minority) of AMSM living in four regions in the United States: (1) Chicago to Detroit, (2) Washington, DC to Atlanta, (3) San Francisco to San Diego, and (4) Memphis to New Orleans.

Results: This project is currently recruiting participants. Recruitment began in March 2018.

Conclusions: iREACH represents a significant innovation in the development and testing of a tailored life skills-focused intervention for AMSM, and has the potential to fill a significant gap in HIV prevention intervention programming and research for AMSM.

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KEYWORDS

prevention; mHealth; adolescence; LGBTQ; sexuality; life skills; HIV

Introduction

Background

Between 2000 and 2010, the annual number of new HIV diagnoses among young men who have sex with men (YMSM; age 13-24 years) in the United States more than doubled [1]. In 2016, youth aged 13 to 24 years made up 21% of all new HIV diagnoses in the United States. Most (81%) of those new diagnoses occurred among young gay and bisexual men. Young black/African American and Hispanic/Latino gay and bisexual men were especially affected [1]. The HIV epidemic among YMSM is characterized by strong racial and ethnic disparities in HIV incidence. Data from the National HIV Behavioral Survey showed 26% of African American youth surveyed (aged 18-24 years) tested HIV positive compared to only 3% of white youth aged 18 to 24 years [2]. Although initially attributed to greater engagement in risk behaviors among racial/ethnic minorities, recent analyses [3-7] illustrate that racial/ethnic disparities in HIV are likely driven by social determinants of health, including access to health insurance and social network properties, and by more limited coverage of effective HIV treatment for those living with HIV. These findings underscore the importance of understanding and addressing the structural factors driving the HIV disparities faced by marginalized YMSM in the United States.

Few HIV interventions have demonstrated efficacy for reducing HIV risk among adolescent men who have sex with men (AMSM). We employ the term AMSM to refer to cisgender males aged 13 to 18 years who may express same-sex attractions and/or engage in same-sex behaviors, yet may or may not identify as gay, bisexual, queer, and/or questioning. AMSM also represent a younger age range than YMSM, which typically includes ages up to 24 years. Mustanski [8] notes that relative to HIV prevention research with adult populations, AMSM have received less research attention, with a paucity of longitudinal studies with follow-up periods of greater than 12 months or the testing of interventions that recognize the unique developmental context of AMSM. Recognizing that AMSM's HIV vulnerability is intricately tied to their developmental stage and social context [9,10], research has posited that delivering life skills training during adolescence may delay the onset of or reduce the consequences of risk. The World Health Organization describes life skills as "the ability for adaptive and positive behavior that enables individuals to deal effectively with the demands and challenges of everyday life." For AMSM, life skills training may include a set of resources tailored to their individual and social contexts, allowing them to learn about and manage their HIV risk. A review [11] concluded that behavioral interventions that teach life skills are highly effective for HIV risk reduction among adult men who have sex with men (MSM); however, there is limited evidence examining whether life skills training for AMSM is an efficacious HIV prevention strategy.

Life skills training programs may be suited to electronic delivery given the proven appeal of e-interventions among youth, the suitability for delivering tailored content specific to each user's HIV risk behaviors and context, and the opportunity to reach AMSM residing in diverse geographic locations [3,4]. Furthermore, given that MSM often rely on online technologies to build their social and sexual networks, receive social support, and obtain relevant health information [12-14], an e-delivered platform may reach AMSM who might otherwise not be able to access LGBTQ+-friendly (LGBTQ+: lesbian, gay, bisexual, transgender, queer, and additional identities) resources and services (eg, rural AMSM). In this protocol paper, we describe our plans to test the efficacy of iREACH, a life skills training Web-based app designed for racially and ethnically diverse AMSM living in four diverse regions of the United States that include rural and urban settings.

Objectives

The primary objective of this randomized controlled trial (RCT) is to test the efficacy of an e-delivered life skills intervention, iREACH, on cognitive and behavioral HIV-related outcomes for AMSM. We will recruit a large and diverse sample of AMSM (N=600; ≤50% non-Hispanic white) living in four regions disproportionately burdened by HIV prevalence across the United States. We have two secondary aims for this project: (1) to examine the differential efficacy of iREACH in shaping the psychosocial mediators (eg, personal competency) associated with our outcomes based on engagement with the intervention, and (2) to explore how socioecological determinants at the individual (eg, race/ethnicity, urbanity) and regional (eg, socioeconomic disadvantage, HIV prevalence) level are associated with intervention efficacy.

Methods

Trial Design

We will conduct a prospective RCT of 600 online-recruited cisgender AMSM (age 13-18 years) followed for 12 months with study assessments at each 3-month interval. A racially/ethnically diverse sample (at least 50% racial/ethnic minority) of AMSM living in four regions in the United States: (1) Chicago, IL to Detroit, MI; (2) Washington, DC to Atlanta, GA; (3) San Francisco, CA to San Diego, CA; and (4) Memphis, TN to New Orleans, LA. Regions were identified by inspection of HIV prevalence rate maps on AIDSvU.org. Eligible counties are those that include the major interstate highway that connects the two anchor cities (ie, I-94 for Chicago to Detroit; I-95 for Washington, DC to Atlanta; I-5 for San Francisco to San Diego; and I-55 from Memphis to New Orleans). Each region includes urban, suburban, and rural counties, as classified by the 2006 National Center for Health Statistics urban-rural classification scheme for counties [15].

Eligibility Criteria

Eligible individuals must (1) have been assigned a male sex at birth and identify as male at the time of enrollment into the study (cisgender male), (2) be between the ages of 13 and 18 years (inclusive), (3) speak and read English, (4) report same-sex attractions and/or behaviors, (5) have access to the Internet, (6) live in one of the zip codes at least partially contained in the 109 counties included in the four regions selected for this trial, and (7) self-report as HIV-negative at time of enrollment.

Recruitment, Screening, Consent, and Enrollment

Potential participants will click on targeted banner advertisements (Figure 1) based on our eligibility criteria (eg, sex, age, region) placed on commonly used social media sites (ie, Facebook), which will direct them to a home page containing basic study information. We will also recruit through community events (eg, LGBTQ+ pride events). Interested individuals will consent to complete an online screener. As part of the screener, we will verify that the participant lives in one of the counties selected for this trial based on their reported zip code. Individuals who do not meet the eligibility criteria will see a screen that thanks them for their interest and provides HIV testing and counseling information and resources. We will not indicate why they were ineligible to avoid unintentional disclosure of their study involvement and to protect against fraud. Eligible individuals will be taken to the study consent form (a waiver of parental consent has been obtained for minor participants). AMSM who do not consent will be taken to a screen thanking them for their interest. AMSM who consent will submit a cell phone number and their cell phone carrier as part of the registration process, an email and/or short message service (SMS) text message containing a code will be immediately sent to verify the user. This process has been found to be acceptable among adolescents [16] and MSM [17,18] in previous studies. After verification, participants will be asked to provide their contact information, including an email address, a cell phone number, social media handles, and a mailing address, and will be asked to provide a nickname or name of

choice to be referred to throughout the study. Participants will then be directed to the baseline survey, which is estimated to take approximately 30 minutes to complete.

Completed baseline survey data and participant information will be manually reviewed and checked for duplications or possible fraud by study staff members. Responses from the screening survey will be checked against responses in the baseline survey (eg, age) to ensure consistency, and IP addresses, email addresses, and phone numbers will be reviewed to check for multiple registrations. Proxy IP addresses will be flagged for further scrutiny, and reviews of the baseline survey data will be conducted to check for suspicious response patterns and realistic completion times. Within 48 hours, participants will receive their log-in credentials, their incentive payment for completion of the baseline survey, and will be assigned in a 1:1 ratio for the intervention or attention control condition using stratified randomization [19] by race and region. Screener and baseline data will be used by iREACH to inform personalized, tailored content for AMSM assigned to the intervention condition.

Intervention Content: iREACH

iREACH (Figure 2) is a tailored Web app intervention for AMSM aged 13 to 18 years. The intervention component of the app aims to facilitate participants lowering their vulnerability to HIV infection by (1) providing life skills educational modules tailored to their unique needs and characteristics, (2) setting goals and encouraging participants to use relevant services available locally to help achieve them, and (3) accessing LGBTQ+–welcoming resources across the life skills areas. Individuals in the experimental arm will have access to iREACH over the 12 months of the study. Within the Web app, they will learn life skills content through activity-based learning across 14 key life areas, set goals in those areas and monitor progress toward these goals, work on these goals using the peer mentor video chat feature, and locate nearby LGBTQ+–welcoming community resources to achieve these goals. We describe iREACH's main components subsequently.

Figure 1. Examples of advertisements used to recruit racial/ethnically diverse adolescent men who have sex with men.

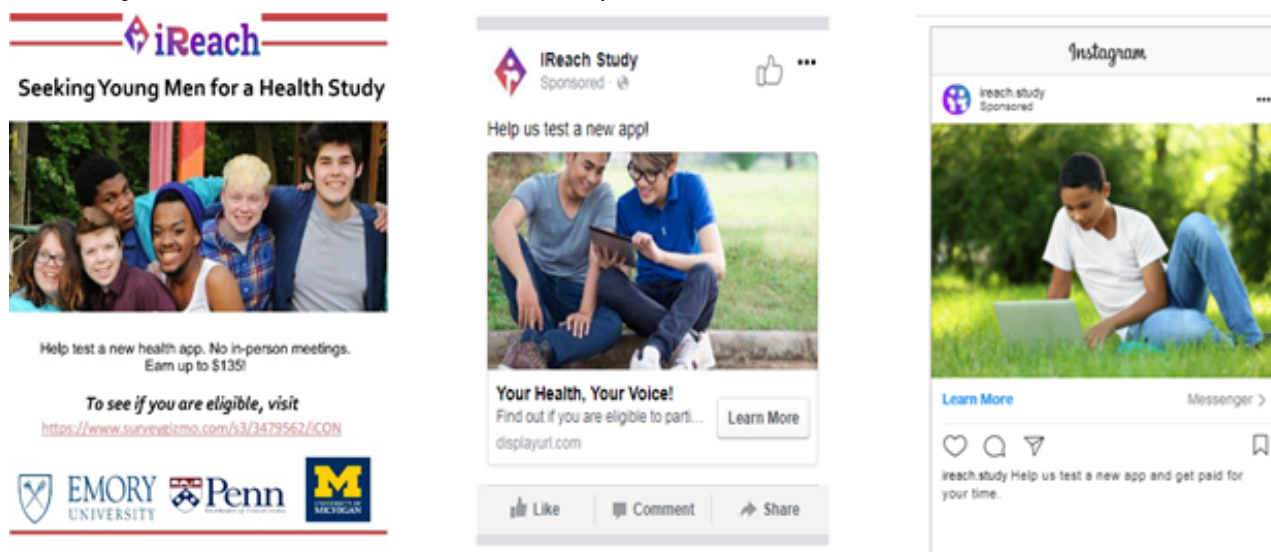
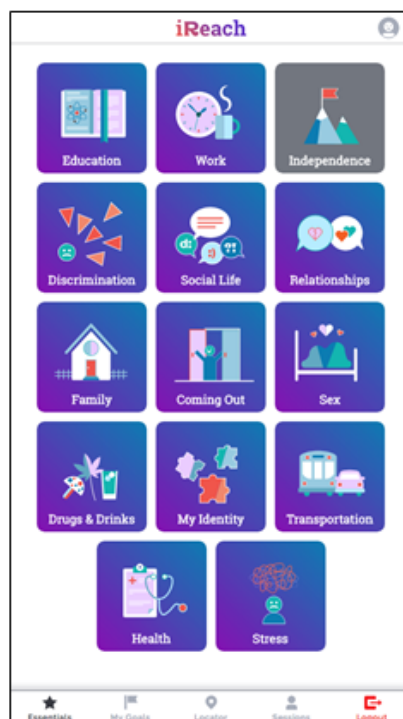


Figure 2. Screen image of iREACH intervention app.

Essentials

The life skills educational content in iREACH covers 14 topics. As shown in [Figure 3](#), content is written at the eighth grade literacy level and presented in an interactive format, which includes infographics, GIF (Graphics Interchange Format) images, interactive activities, and accordion (drop-down) headers to improve the ease of navigation and level of cognitive effort. Tailored (ie, personalized) content is derived from AMSM's baseline sociodemographic characteristics (eg, age, region) and answers to follow-up surveys inform new personalized content. For example, although we will only enroll participants who identify as male at baseline, iREACH is responsive to the gender development of AMSM during the study: if a participant identifies as transgender or gender nonconforming during the intervention, they can edit their profile name and preferred pronouns. Similarly, if a participant reports being newly diagnosed with HIV during the study, iREACH is designed to provide HIV-specific content (eg, how to keep up with their treatment plan, how Ryan White funds can assist with medication, transportation, and social support).

Goal Setting

Participants will be able to set, monitor, and track their goals through the "My Goals" component of the Web app. The variety of possible goals is based on AMSM's wide range of potential needs and experiences across the four regions. As shown in [Figure 4](#), participants select the primary goal (eg, autonomy, competence, relatedness, and self-actualization) they wish to work on, followed by the relevant life skills domain (eg, work, relationships, and sex). Participants can then select from a list of prepopulated common goals or can create their own goal, and determine whether it is a short-term (now), medium-term (soon), or long-term (later) goal. Using a progress navigation bar, participants can track their progress on their goals ([Figure](#)

5), delete goals that are no longer relevant, and review goals marked as completed. Participants may also review and receive feedback on their goals through peer mentor sessions (described subsequently).

Local Resources

Participants who click on the "Locator" button will access a prepopulated list of national (eg, crisis hotlines) and local resources (eg, gay-straight alliances, HIV testing locations). We identified 1833 eligible resources across our four study regions; each resource was verified through mailers and phone calls using protocols adapted from HIV testing [20] and pre-exposure prophylaxis (PrEP) [21] locators. A random subsample (20%) of resources will be selected for review every 6 months and updated as necessary.

The Locator section filters resources for the participants' regions automatically and clusters the resources linked to each life skill area. Participants can further refine the resources based on their county, zip code, and/or current distance to the resource (as computed by their browser's geolocation if activated). If a local resource does not exist in their area or if a participant moves out of the designed regions during the study, the Locator will provide national hotlines and websites. We detail the proportion of services identified, verified and included in our Locator in [Table 1](#).

Peer Mentors

Building on the Web app's life skills content and goal-setting structure, iREACH acknowledges that AMSM's achievement of these goals can be enhanced by role playing and coaching. LGBTQ+ supportive peers may be limited in some communities; therefore, iREACH provides participants with access to trained peer mentors who can help AMSM personalize the life skills lessons, set new goals and/or support those already identified,

and provide peer-to-peer social support. Participants can schedule and attend these peer mentor appointments (approximately 30 minutes, on average) through the “Sessions” button.

These sessions are housed within the VSee video chat telemedicine platform, accessible from their Web app. AMSM concerned about privacy may use VSee in four ways: (1) video in which both they and the peer mentor can be seen, (2) video in which only the peer mentor can be seen, (3) audio only, or (4) a text-only chat interface. Peer mentors (YMSM aged 18-29

years) will be trained to use motivational interviewing principles in their exchanges with AMSM, and supervised by study team members experienced in motivational interviewing and counseling (eg, psychologist, professional counselor). Peer mentors will use a social problem-solving approach to help participants set goals that are achievable and moderately challenging and to identify potential solutions to problems. Participants will be able to schedule a maximum of three sessions per week. This service will be available throughout the full year of their assignment to the intervention.

Figure 3. Screen images of iREACH intervention app illustrating age-appropriate literacy and interactive format. SO: significant other.

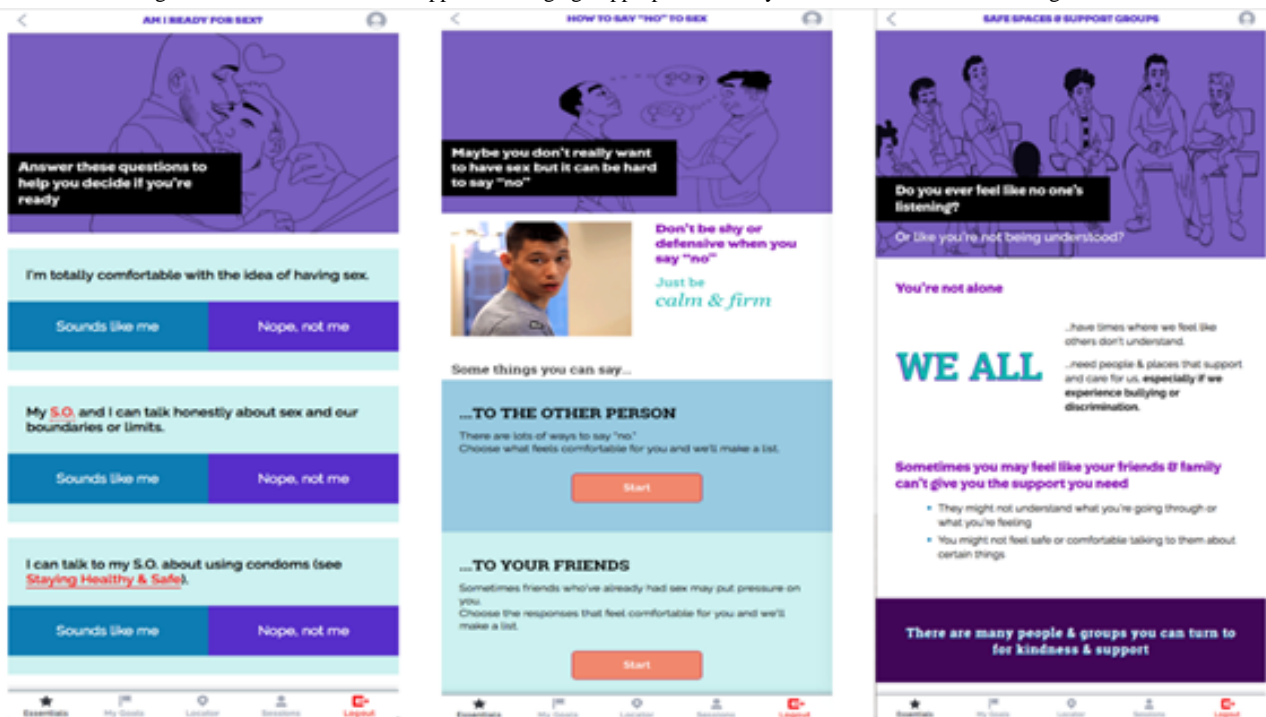


Figure 4. Screen images of iREACH intervention app illustrating goal-setting activities.

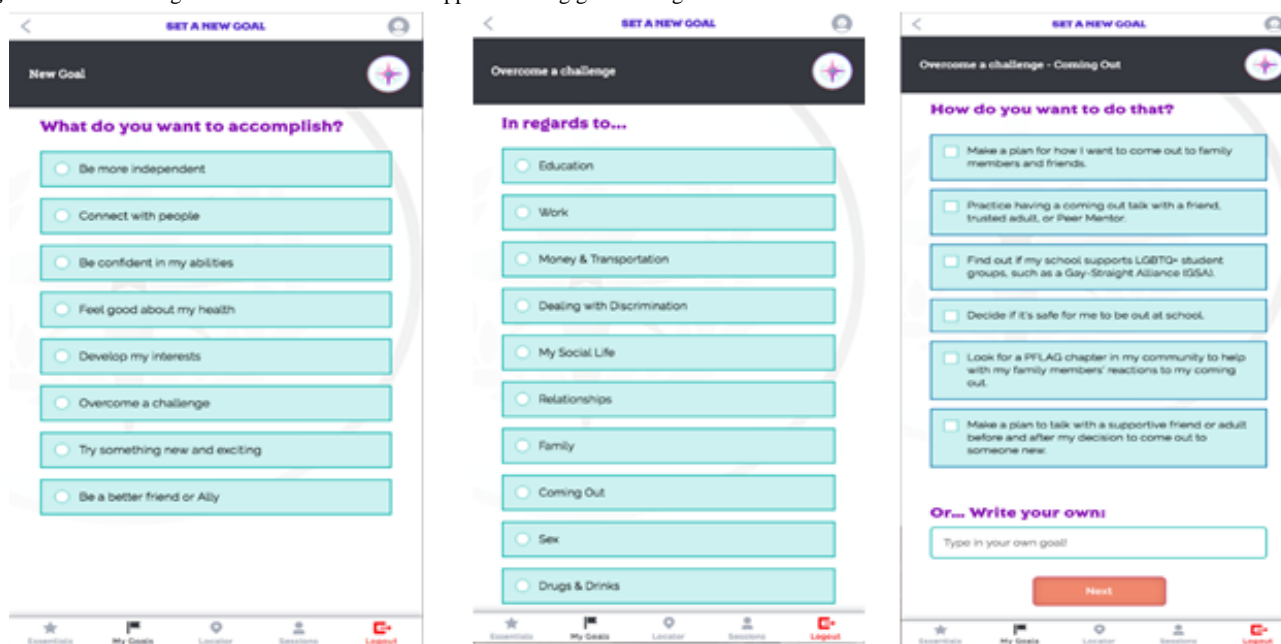


Figure 5. Screen image of iREACH intervention app illustrating goal progress tracking.**Table 1.** Number of local resources identified and included in the iREACH locator by region^a.

Region	HIV services, n (%)	Mental health and substance use, n (%)	LGBTQ+ ^b resources, n (%)	Food pantry, n (%)	Shelters and housing, n (%)	Intimate partner violence resource, n (%)	Total resources in region (N=1933), n (%)
Chicago, IL to Detroit, MI	376 (47.1)	472 (59.1)	152 (19.0)	31 (3.9)	91 (11.4)	103 (12.9)	798 (43.5)
Washington DC to Atlanta, GA	233 (43.7)	317 (59.5)	123 (23.1)	16 (3.0)	31 (5.8)	37 (6.9)	533 (29.1)
San Francisco, CA to San Diego, CA	154 (47.0)	239 (72.9)	81 (24.7)	11 (3.4)	28 (8.5)	32 (9.8)	328 (17.9)
Memphis, TN to New Orleans, LA	86 (50.6)	82 (48.2)	7 (4.1)	6 (3.5)	8 (4.7)	9 (5.3)	170 (9.3)
National hotlines	0 (0.0)	3 (75.1)	3 (75.4)	2 (50.4)	1 (25.2)	2 (50.3)	4 (.22)

^aResources often offer multiple types of services; percentages reflect the proportion of local resources offering a specific type of resource. Regions comprise all counties touching the major interstate corridor connecting the two anchor cities.

^bLGBTQ+: lesbian, gay, bisexual, transgender, queer, and additional identities.

Additional Engagement

To promote on-going user engagement, intervention participants will also gain badges (Figure 6) to reinforce continued participation on the site [22,23]. Badges are unlocked as participants complete tasks on the Web app (eg, setting goals, reading content, scheduling peer mentor sessions), and continuously engage in the site (eg, returning to the Web app, using it on weekdays and/or weekends, logging on the site on different hours of the day). Participants also can access a message board where they can start and discuss topics with each other. Peer mentors will monitor these boards and facilitate discussions as needed.

Information-Only Attention Control Arm

Those AMSM assigned to the attention control arm (N=300) will only receive access to the “Locator” component of the intervention (Figure 7). Although the provision of a service locator is a form of an intervention, albeit weak, and it may decrease our ability to detect intervention effect, we felt that withholding referrals to services would be unethical given AMSM’s vulnerability to HIV and sexually transmitted infections (STIs). At the end of the RCT, participants in the attention control condition will be given full access to the iREACH intervention for 3 months.

Figure 6. Screen image of iREACH intervention app illustrating badge earning.

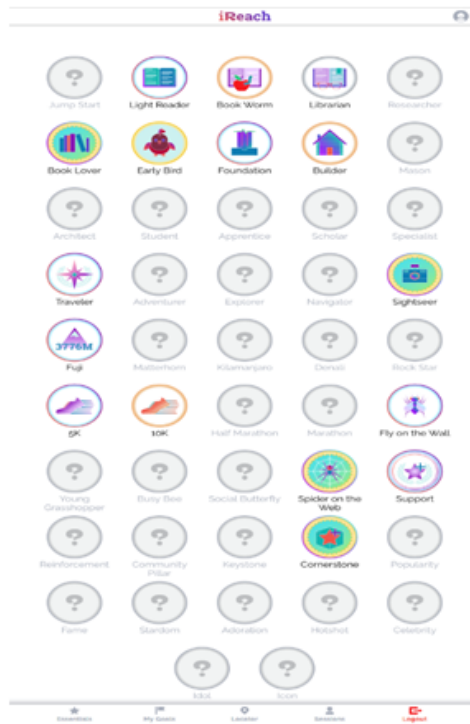
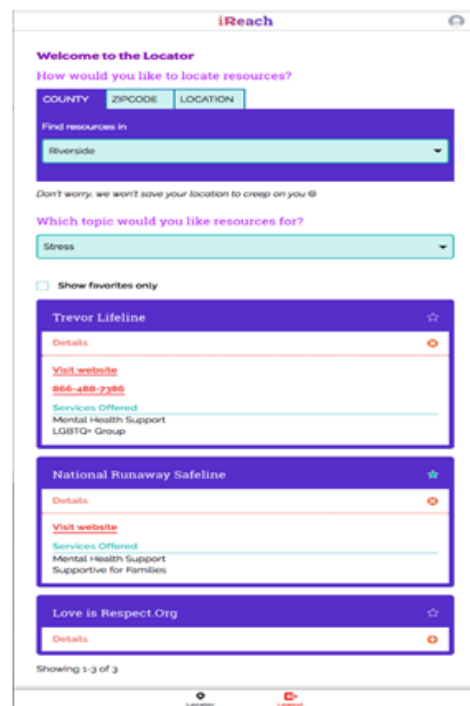


Figure 7. Screen images of information-only attention control condition illustrating service locator information.



Outcomes

Because our participants will be ages 13 to 18 years and many might not have begun sexual activity or used HIV prevention services, we set our primary outcomes as cognitive factors linked to the ability to use HIV prevention and behavioral intentions to use HIV prevention. Our secondary outcomes are behavioral factors. Cognitive factors can be measured for all AMSM, regardless of whether they have initiated sexual activity with partners, and are broadly grouped into (1) knowledge, (2)

attitudes, (3) norms, (4) self-efficacy, and (5) perceived behavioral capacity. Behavioral intention outcomes include self-reported intentions to adopt HIV risk reduction strategies and HIV prevention services. We also include secondary outcomes that apply to the subset of AMSM who are sexually active, and include self-reported HIV risk-taking behavior (both sexual and drug/alcohol use) and the use of HIV prevention services (eg, testing) and prevention activities (eg, abstinence, condoms, PrEP). We detail study measures in Table 2.

Table 2. Measures planned for a randomized controlled trial of a life skills intervention for adolescent men who have sex with men in the United States.

Domain	Assessment time					
	Baseline	Month 3 ^a	Month 6	Month 9	Month 12	Month 15 ^b
Primary outcomes						
HIV knowledge [24]	X		X		X	X
Condom use/communication efficacy [16]	X		X		X	X
HIV/STI testing	X		X		X	X
Outcomes required for analysis						
Demographics	X		X		X	X
Patient provider communication around sexual orientation [25]		X		X		
Stigma [26]		X		X		
Resilience [27]		X		X		
Psychological needs [28]	X		X		X	X
Future life goals [29]		X		X		
Secondary outcomes						
Internalized homonegativity [30]	X		X		X	X
PrEP use and willingness [31]	X		X		X	X
Sex behaviors [32,33]	X		X		X	X
Substance abuse [34,35]	X		X		X	X
Depression [36]	X		X		X	X
Anxiety [37]	X		X		X	X
Self-Esteem [38]	X		X		X	X
Covariates						
Peer influence [33]		X		X		
Family support [39]		X		X		
Discrimination [40]		X		X		
Online behaviors [41,42]		X		X		
Societal reaction to sexual orientation [43]		X		X		
Ethnicity beliefs [44]		X		X		
Relationship history [45]	X		X		X	X
Intervention acceptability [46,47]		X				X

^aThe iREACH intervention question set will only be available to the intervention group for month 3.

^bOnly participants initially assigned to the control condition will complete survey at month 15 after receiving access to the iREACH intervention.

Incentives

Participants receive US \$30 for the baseline and 12-month follow-up and US \$25 for the 3-, 6-, and 9-month follow-ups. Control participants will receive US \$30 for completing the 15-month follow-up. These incentives are small enough to avoid coercion, yet sufficiently substantial to promote retention.

Recruitment and Randomization

Sample Composition

We used Census information on population structure by race/ethnicity for each region to inform our recruitment goals.

Briefly, using 2010 Census data, we calculated the number of men in the eligible age group and by race/ethnicity in each region (Table 3). We then used data from the Youth Behavioral Risk Factor Surveillance System [48] to estimate the proportion of AMSM in each age group who could meet eligibility criteria based on same-sex behavior, identity, or attraction for our study, and applied that age-specific proportion to the estimated total AMSM population by race in each region. This resulted in an estimated number of eligible AMSM per region and racial/ethnic group. Within each region, we calculated a proportional recruitment target under the assumption that the 150 AMSM in that region would be recruited proportional to their population prevalence.

Table 3. Estimated eligible adolescent men who have sex with men by race and ethnicity and proportional and planned study enrollment for each region.

Race/ethnicity	Region ^a , n												Total ^b
	San Francisco/San Diego			Atlanta/Washington, DC			Detroit/Chicago			Memphis/New Orleans			
	Est ^c	Prop ^d	Goal ^e	Est	Prop	Goal	Est	Prop	Goal	Est	Prop	Goal	
Hispanic	41,515	49	29	5732	16	29	6186	23	29	742	8	28	115
White	59,424	70	32	30,531	84	31	21,777	82	31	6974	75	31	125
Black/African American	6434	8	42	13,488	37	38	9053	34	37	5805	62	38	155
Asian	14,185	17	12	2988	8	12	1822	7	13	268	3	13	50
American Indian or Alaska Native	664	1	11	168	1	13	112	1	13	28	0	13	50
Native Hawaiian/Other Pacific Islander	362	0	11	24	0	13	0	0	13	1	0	13	50
Multiracial	4349	5	13	1355	4	14	888	3	14	202	2	14	55
Total	126,933	150	150	54,286	150	150	39,838	150	150	14,020	150	150	600

^aRegions comprise all counties touching the major interstate corridor connecting the two anchor cities.

^bTotals within race/ethnicity groups may not sum to total planned enrollment due to rounding.

^cEst: estimate. Estimated total adolescent MSM (aged 13-18 years) in the region who have same-sex sexual experience, same-sex attraction, or are gay/bisexually identified.

^dProp: proportion. Reflects the target recruitment for each racial/ethnic subgroup, assuming that enrollment is evenly distributed by region, and proportionally distributed by population prevalence of eligible AMSM within region.

^eGoal: trial recruitment goal.

To recruit a sample that is diverse in terms of race/ethnicity, we will need to substantially oversample some racial/ethnic subgroups based on these calculations. To achieve a sample that is 50% or more nonwhite adolescent men, we will oversample Hispanic AMSM by a factor of 1.2, Asian MSM by a factor of 1.5, multiracial AMSM by a factor of 3.8, Native American AMSM by a factor of 25.6, and Native

Hawaiian/Pacific Islander MSM by a factor of 100 (Table 4). Therefore, we have budgeted more resources for recruitment in these subgroups, and will direct substantial recruitment focus toward these groups through selection of race/ethnicity concordant models in advertisements and through identifying community events or support groups that are especially relevant to these subgroups [49].

Table 4. Overall recruitment goals of adolescent men who have sex with men (AMSM) based on allocation based on population prevalence, planned recruitment, and ratio of planned to proportional allocations for a randomized controlled trial of a life skills intervention.

Race/ethnicity	Proportional ^a , n	Planned ^b , n	Relative recruitment ^c , n
Hispanic	96	115	1.2
White	311	125	0.4
African American/black	141	155	1.1
Asian	35	50	1.5
American Indian or Alaska Native	2	50	25.6 ^d
Native Hawaiian/Other Pacific Islander	1	50	>100.0 ^d
Multiracial	14	55	3.8 ^d
Total	—	600	—

^aProportional recruitment is determined by multiplying the estimated proportion of all AMSM in the four regions by the total study enrollment (N=600).

^bPlanned enrollment is an empirically determined set of requirement targets.

^cRelative recruitment is the ratio of the planned/proportional recruitment numbers, representing the relative under- or overrepresentation of the population in the planned sample, relative to their representation in the overall population of the study areas.

^dThese relative recruitment values are calculated from proportional recruitment numbers with more precision than those displayed in the proportional column (eg, for Native Hawaiian/Other Pacific Islander, the proportional sample is calculated as 0.0016 person, but it is depicted as 1 since fractional recruitment of participants is not possible). Therefore, the relative recruitment differs from the simple ratio of the planned to proportional for these groups.

These data also make clear that the distribution of participants will not be equal across the four geographic regions within racial/ethnic groups; therefore, we will stratify randomization within race and region. Based on estimated AMSM population sizes and historical data on sampling fractions, we anticipate more than 35% of participants will come from rural areas [50]. We recognize the challenge of recruiting early adolescents given that same-sex attraction and same-sex sexual experience become more common with age. Therefore, we realistically expect to include a greater number of participants in the older age range.

Recruitment

Recruitment will utilize both virtual and physical venues. Targeted advertisements, representing age and ethnic diversity, will be promoted on Facebook, Instagram, Snapchat, and organizational websites. In addition, supplemental advertising on other social media platforms (YouTube, Tumblr, Twitter, and Reddit) may be used to expand recruitment efforts. The social media campaigns will be monitored and adjusted throughout the recruitment phase. Across all regions, physical recruitment materials will be developed and distributed among organizations that serve and support LGBTQ+ youth (eg, homeless youth organizations, community LGBTQ+ centers, HIV resources). Physical recruitment materials will also be distributed during large community events, including pride festivals in the study regions.

Strategies to Ensure Sample Diversity

We will develop ads that promote AMSM's interest by including diverse images of youth (Figure 1) and targeting specific sociodemographic characteristics and interests.

During the formative phase of the study, facilitated focus group discussions were conducted online to identify the most effective recruitment strategies to optimize diversity and to ensure that culturally appropriate strategies are employed to engage and retain enough Asian/Pacific Islander, Native American, and Alaskan Native participants. These include promoting the study to agencies, social media groups, and in social media forums highly utilized by youth in these specific ethnic groups, and incorporating recruitment messages that encourage community engagement. Materials will avoid identifying candidates as AMSM in the recruitment text to avoid unintended disclosure.

Retention

To be evaluated as potential "best-evidence" interventions through the Centers for Disease Controls and Prevention's Prevention Synthesis Research activity [51], data must be available for at least a single follow-up time point for more than 70% of participants. As indicated subsequently, a detailed retention plan for the study will draw on previously successful retention protocols to achieve 80% or more retention at the first follow-up visit. We will use successful best practices from previous studies [17,49] to retain participants (eg, comprehensive locator information that includes participants' cell phone number, email, Facebook and/or other social media usernames), while being sensitive to undue disclosure of AMSM participating in the study. In addition, we allow participants to specify the day of the week and time of day when they would like to receive electronic follow-up surveys [17].

We have a preplanned schedule of follow-up assessments utilizing a variety of methods. Initially, a respondent who does not respond to an electronic notification that a survey is due will automatically receive additional notifications 48 hours after the initial notification the survey is available. If the participant has still not completed the assessment 7 days after the third electronic notification, the retention activities are escalated to a research staff member who will use the participant's contact preferences provided on registration (eg, by SMS text message). If still unresponsive, other available contact information (eg, phone call) will be used. Each contact is logged in an electronic retention system (Study Management and Retention Toolkit [SMART]) developed by Emory University [17,18,52]. The SMART system also maintains electronic lists of participants' retention status, and automatically creates notification lists for retention staff to ensure that a systematic process is followed and carefully documented for retention.

Statistical Methods

The primary outcome analyses seek to test the efficacy of iREACH compared to the information-only control condition to improve cognitive factors and behavioral intentions (eg, comfort discussing sexuality, HIV prevention attitudes, norms, self-efficacy) and behavioral factors (eg, condom use, HIV testing, PrEP use). Psychosocial and demographic characteristics will be described for all participants and by intervention group. These will be compared between treatment groups using *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. We will determine from the analyses stratified by treatment arm whether or not a failure of randomization occurred. We will use the general framework of generalized linear mixed models to test for intervention effects over time. For some binary outcomes, such as HIV testing, we will perform an aggregate analysis after collapsing across the repeated measures using simple logistic regression comparing whether the probability of having tested at least once over the entire follow-up period is different across treatment groups. To ensure robustness, we will also apply an exchangeable working correlation structure to its corresponding generalized estimating equation model.

Sample Size and Power Calculations for Primary Analyses

Our expected sample size for analyses across both conditions is $N=600$ (intervention: $n=300$; control: $n=300$), assuming a 15% to 20% loss to follow-up. We estimated the minimum detectable effect sizes at 80% power, for comparisons of the two groups for the primary cognitive and behavioral intentions outcomes. For mean differences, our sample size calculations are based on a two-sample *t* test assuming equal variance using a two-sided significance of .05. At 80% power, we can detect a between-arm difference of $d=0.22$ at the final follow-up. For repeated measure analyses, assuming a within-person correlation of .25, we would be able to detect a difference of 0.08. For proportions, our sample size calculations are based on a two-sample test of proportions using a two-sided significance of .05. To have 80% power to compare the intervention to the control group, we require at least 500 participants to find a 12.5% difference between arms in cross-sectional analyses.

Assuming within-person correlation of .25, we can detect an 8.8% difference.

Secondary Analysis

To examine the effects of our intervention on the psychosocial correlates (eg, personal competence), we will run a regression with only group assignment in the model. Among participants assigned to the intervention arm, we will test whether the intervention effects vary as a function of AMSM's varying engagement with the intervention as measured by paradata metrics (eg, frequency of site log-ins, time spent on intervention components). Among participants assigned to the control arm, we will describe AMSM's varying engagement with the resource guide as measured by paradata metrics (eg, frequency of site log-ins) and test whether engagement is associated with changes over time within the control arm. Finally, we will use multilevel models to examine how regional characteristics influence AMSM's outcomes [53]. We will link individual and regional level data using participants' residential address at enrollment. Our regional unit of analysis will be county-level to ensure enough participants per region and to avoid inadvertent identification of participants. Exploratory analyses will examine whether county-level characteristics (eg, economic disadvantage, racial composition, HIV prevalence) are associated with individual-level outcomes. Analyses will be adapted for binary, count, or continuous outcomes accordingly.

Intervention Exposure, Fidelity, and Dosage

We will measure intervention exposure using paradata from the intervention, including counts of user sessions, session lengths, pages visited, and functions utilized [54]. For the peer mentor component, we will record the number and duration of peer mentor sessions, as well as the domains covered in these sessions. This information will assist in examining whether intervention dosage influences the efficacy of the intervention, and inform wider implementation and scalability.

Results

The protocol has been reviewed and approved by the University of Pennsylvania Institutional Review Board (825686) and is registered on ClinicalTrials.gov (NCT03155841).

This project is currently recruiting participants. Recruitment began in March 2018.

Discussion

Limitations and Anticipated Challenges

There are several potential challenges to the success of our trial. First, we propose to recruit a diverse (in terms of race/ethnicity, rurality, and socioeconomic status) sample of adolescents aged 13 to 18 years. This poses two potential challenges. First, we may experience more success in recruiting AMSM at the older ages of this range (eg, 16 years and older). To counteract this challenge, we have elicited feedback from AMSM during our formative planning and have planned for a broad range of social media outlets utilized commonly by these age groups in our recruitment. We will also leverage youth-focused social media outlets in each of the four sampled regions when available.

Second, we recognize that AMSM living in the urban centers of each of our sampled regions and/or who are non-Hispanic white might be easier to recruit into the study. There is now strong evidence of high levels of Internet, personal computer, and mobile phone use across all race and ethnic groups [41], indicating that our modes of recruitment should not bias toward any particular demographic. We will ensure racial and ethnic representation in all advertising. Many social media outlets allow advertising targeted by zip codes, allowing us to target recruitment ads to all zip codes in each of our sampled regions. We will monitor the characteristics of our enrolled sample closely; if we are enrolling urban youth at a faster pace than rural youth then we will increase our advertising efforts in rural zip codes. Third, given time and resource constraints, our intervention focuses on English-speaking AMSM. Although this decision may exclude Spanish-only speakers, recent Census data suggests that 88% of Hispanic youth younger than 17 years in the United States are proficient in English [55]. If the intervention is found to be efficacious, we will explore opportunities to translate the intervention. Fourth, there is a possibility that peer mentor sessions may be popular among AMSM and might require us to increase the number of available slots per day. If so, we will adjust our schedule and hire/train new peer mentors to meet the demand. Finally, we are vigilant of events that may lead to unintended disclosure of sexuality, behavior, and research participation to the participant's parents/guardians. To minimize the possibility of unintended disclosures, we have integrated widely used Web privacy features, such as password authentication, automatically logging users out after a period of inactivity, and not including sensitive details in communications sent to participants. We have also structured the intervention to give participants some control over their own privacy, such as allowing them to indicate preferred methods of receiving communication (ie SMS text message, email, or social media private message), and remind participants to be active in protecting their information. If a parent or guardian becomes aware of AMSM's participation in the trial and chooses to reach out to the study team, a member of the research team will be available to speak with the parent/guardian; however, to protect AMSM's privacy, we will not confirm their child's participation in the trial or share data with parents.

Conclusions

As the numbers of HIV-infected AMSM continue to grow, innovative methods to scale up HIV prevention to AMSM are required. A life skills intervention delivered to a diverse sample of AMSM may reduce the existing HIV disparities across social categories (eg, race/ethnicity, rurality, socioeconomic status) by promoting equitable access to psychosocial and sexual health resources, and by reducing HIV-related risk factors that may be learned in adolescence and sustained across adulthood. The tools and framework used in this project may be directly applicable to US-based studies of this population. Along with promoting HIV risk reduction, our most significant contribution will be the development of an online intervention that builds on AMSM's life skills and addresses the psychosocial needs during this developmental period. In fact, given the dearth of studies focused on AMSM, our trial may represent one of the

first systematic evaluations of a psychosocial and behavioral intervention for this age group.

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Conflicts of Interest

None declared.

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Abbreviations

- AMSM:** adolescent men who have sex with men
- LGBTQ+:** lesbian, gay, bisexual, transgender, queer, and additional identities
- MSM:** men who have sex with men
- RCT:** randomized controlled trial
- SMART:** Study Management and Retention Toolkit
- SMS:** short message service
- STI:** sexually transmitted infections
- YMSM:** young men who have sex with men

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Protocol

Enzalutamide Versus Abiraterone as a First-Line Endocrine Therapy for Castration-Resistant Prostate Cancer: Protocol for a Multicenter Randomized Phase 3 Trial

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Abstract

Background: Recent large-scale randomized studies have demonstrated that 2 new hormone preparations (abiraterone and enzalutamide) prolong survival in docetaxel-treated or -naïve castration-resistant prostate cancer patients. However, no studies have directly compared antitumor effects between these 2 agents, and no clear guidelines are available for choosing between them.

Objective: The objective of this clinical study is to compare antitumor effects and adverse events between abiraterone and enzalutamide by allocating castration-resistant prostate cancer patients deemed not indicated for docetaxel treatment to receive either of the 2 agents.

Methods: This study is an open-label, comparative study allocating castration-resistant prostate cancer patients to abiraterone or enzalutamide treatment arms (allocation factors: age <70 vs ≥70 years, and presence vs absence of metastases) and assessing the treatment results. Each arm will contain 25 patients. On confirmation of prostate-specific antigen failure or progression on imaging, patients undergo crossover to receive the alternative study drug. The primary end point is prostate-specific antigen response rate (percentage of patients with a decrease in prostate-specific antigen level by ≥50%) in the abiraterone and enzalutamide treatment arms.

Results: Recruitment started in May 2016, and 13 patients have been recruited so far. We expect to complete enrollment by December 2020.

Conclusions: Recently, cross-resistance between abiraterone and enzalutamide has been an issue of focus. Urologists thus tend to prefer docetaxel rather than sequential therapies using 2 hormonal preparations after the progression of a first hormonal preparation. From that perspective, our clinical trial is rather out of fashion. Nevertheless, we assume that many patients receive hormonal sequential therapy in the actual clinical setting, since most such patients cannot receive chemotherapeutic agents due to old age or poor performance status. This is why we are attempting this randomized clinical trial comparing abiraterone versus enzalutamide. We will try to identify which drug is suitable for initial hormonal therapy among castration-resistant prostate cancer patients who do not meet the indications for docetaxel therapy in terms of not only antitumor effect, but also adverse events and quality of life.

Trial Registration: University Hospital Medical Information Network UMIN000022102; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000025463 (Archived by WebCite at <http://www.webcitation.org/70xaQfGIJ>)

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KEYWORDS

castration resistant prostate cancer; abiraterone; enzalutamide; prostatic neoplasms, castration-resistant; clinical protocols

Introduction

Hormone therapies are considered beneficial for the treatment of advanced prostate cancer [1]. In fact, hormone therapies are known to be safe and highly effective, but the biggest drawback is the lack of sustained antitumor effects [1]. Scientists have long been frustrated in attempts to find pharmacotherapies, including anticancer agents, that would prolong survival among patients with prostate cancer that has acquired resistance to hormone therapies (castration-resistant prostate cancer [CRPC]).

In 2004, docetaxel became the first anticancer agent confirmed to prolong survival in CRPC patients in 2 large-scale clinical trials [2,3] and was adopted as the first-line treatment for CRPC in Japan. In addition, recent large-scale randomized studies have demonstrated that 2 new hormone preparations (abiraterone and enzalutamide) prolong survival in docetaxel-treated [4,5] or -naïve CRPC patients [6,7]. Clinical use of the 2 agents in Japan began in 2014. While these 2 hormone preparations (abiraterone and enzalutamide) have different mechanisms of action, both exhibit strong inhibitory effects on the remaining androgen after androgen-deprivation therapy, leading to antitumor effects. However, to our knowledge, no studies have directly compared antitumor effects between these 2 agents, and clear guidelines are lacking for choosing between them.

The objective of this clinical study is to compare antitumor effects and adverse events between abiraterone and enzalutamide by allocating CRPC patients deemed to not meet the indications for docetaxel treatment to receive either of the 2 agents.

Methods

Study Patients

Inclusion Criteria

First, participants in the study are CRPC patients after concomitant antiandrogen therapy with at least a single agent who are docetaxel naïve and deemed to not meet the indications for docetaxel treatment (regardless of the presence or absence of metastasis). CRPC is defined as an increase in prostate-specific antigen (PSA) that is 25% or more and 2 ng/mL (2 µg/L) or more over the nadir PSA level obtained on measurements taken at least 4 weeks apart, with the day of CRPC confirmation defined as the day of relapse (day of disease progression). Testosterone level is measured at the same time to confirm that the level is no higher than the castration level (ie, <50 ng/dL or 1.7 nmol/L). The first-line therapy will be a docetaxel-prednisolone therapy for patients with a Gleason score of 8 or higher and multiple bone metastases for whom the duration of response to a hormone therapy is short (approximately standard, within 2 years) and whose systemic conditions can more than withstand docetaxel-prednisolone therapy.

Second, participants' absolute PSA level is 5 ng/mL (5 µg/L) or higher. Third, participants are less than 85 years of age.

Fourth, participants have an Eastern Cooperative Oncology Group Performance Status of 0 to 2 and expectation of survival 3 months or longer. Fifth, participants have normal organ function, with a white blood cell count of 3000/mm³ or greater or a neutrophil count of 1500/mm³ or greater; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations less than 1.5 times the institutional upper limit; and serum creatinine concentration less than 1.5 times the institutional upper limit. Sixth, participants have personally provided written informed consent to participate in the study.

Discontinuation Criteria

If discontinuation of the study drug administration is deemed justified due to a serious adverse event or when any of the following criteria are met, the investigator shall discontinue study drug administration at their discretion and record in the case report form the reasons for discontinuation and the findings available at discontinuation: (1) study continuation is deemed difficult due to disease progression (PSA recurrence or clinical recurrence); (2) study continuation is deemed difficult due to an adverse event; (3) grade 4 toxicities have occurred as assessed by the Japanese Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by the Japan Clinical Oncology Group and Japan Society of Clinical Oncology [8]; (4) the participant or a family member has withdrawn consent or requested to discontinue the study treatment; (5) study continuation is deemed difficult due to an unforeseen incident; or (6) study continuation is deemed difficult by the investigator due to any other reason.

Dose-Reduction Criterion

In cases of mild adverse events, the dose of the study drug may be halved and then gradually increased or decreased depending on the condition of the participant.

Study Design

The study is an open-label, randomized comparative study that allocates CRPC patients to an abiraterone treatment arm or an enzalutamide treatment arm (allocation factors: age <70 vs ≥70 years, and presence vs absence of metastases) and will assess the treatment results. Figure 1 shows a flowchart of the study design.

Patient Enrollment

The patient enrollment center is at the Clinical Research Center, Wakayama Medical University.

Enrollment Procedure

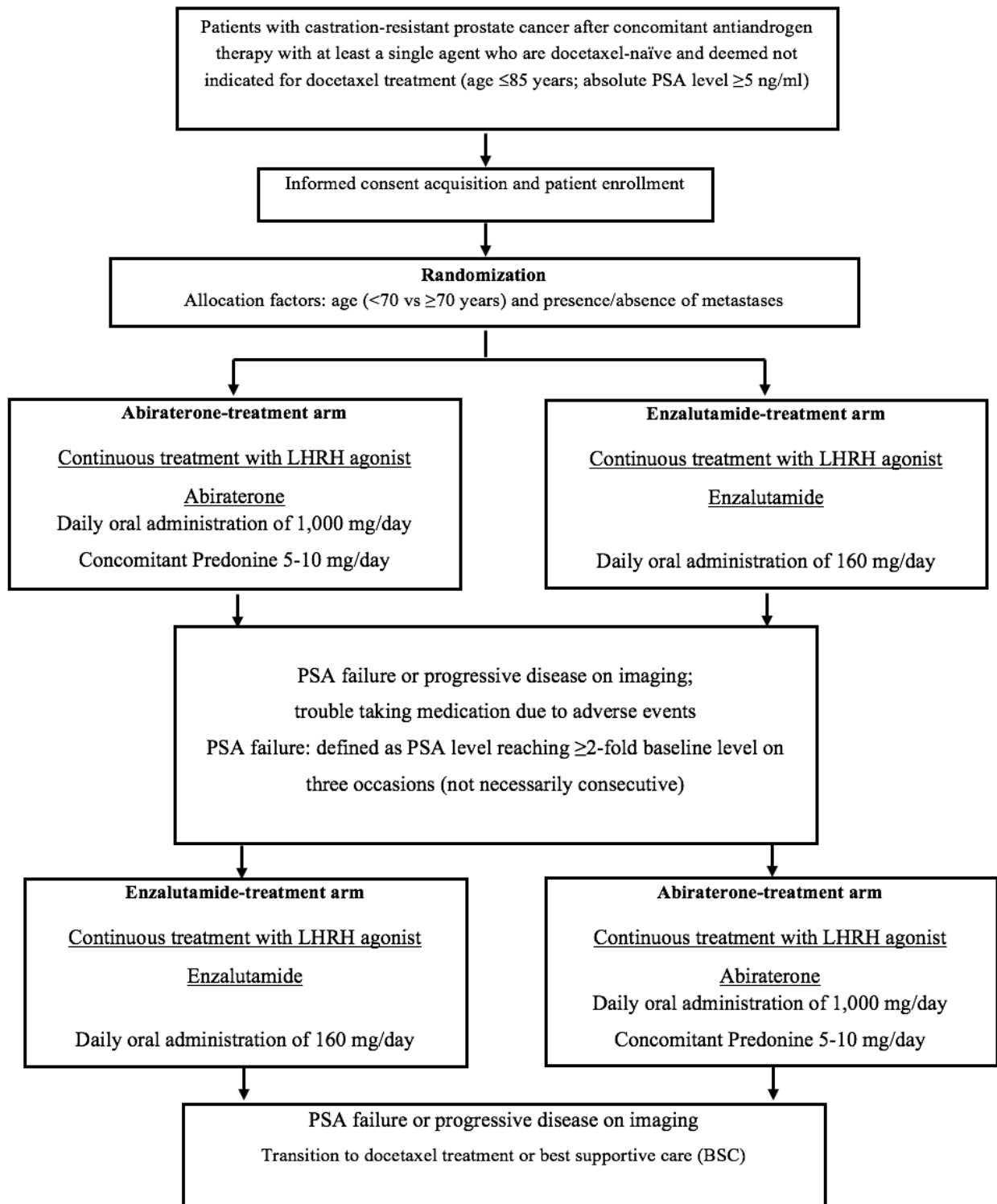
The investigator checks that candidate patients conform with the inclusion criteria and enrolls patients according to the following procedure. (1) Acquire written consent from the patient, complete the required information on a patient enrollment sheet, and transmit the sheet by facsimile to the patient enrollment center. (2) The patient enrollment center checks the information provided on the patient enrollment sheet for eligibility, enrolls the patient, and allocates the patient to a

treatment arm. The patient enrollment center sends the investigator a patient enrollment notification that provides information on the allocated treatment. (3) The investigator checks the patient enrollment notification sent by the patient enrollment center and initiates administration of the allocated treatment drug.

Random Allocation and Stratification Factors Used for Allocation

The patient enrollment center randomly allocates patients to either the abiraterone treatment arm or the enzalutamide treatment arm in a 1:1 ratio. We use the factors of (1) age (<70 vs ≥ 70 years) and (2) presence or absence of metastases as stratification factors for random allocation.

Figure 1. Clinical trial flowchart. LHRH: luteinizing hormone-releasing hormone; PSA: prostate-specific antigen.



Treatments

Hormone Therapy

Surgical castration or treatment with a luteinizing hormone-releasing hormone agonist (either leuprorelin acetate or goserelin acetate) continues even after diagnosis of CRPC.

Study Drugs

Abiraterone

Abiraterone (Zytiga 250 mg tablets; Janssen Pharmaceutica NV, Beerse, Belgium) is a prostate cancer therapeutic agent (cytochrome P450 [CYP] 17 inhibitor). Usually, for adults, it is administered in a dose of 1000 mg orally as abiraterone acetate, once daily under fasting conditions concomitantly with prednisolone. The precautions related to dosage and administration are as follows. (1) Food causes an increase in the maximum concentration and area under the curve for abiraterone. As a result, abiraterone should not be taken from 1 hour before to 2 hours after a meal (refer to the Pharmacokinetics section of the patient package insert). (2) The researcher administering prednisolone should be familiar with the information in the Clinical Results section of the patient package insert. (3) In cases of elevated values for liver function tests while a patient is undergoing abiraterone treatment, abiraterone should be temporarily interrupted, reduced in dose, or discontinued with the following guidelines as a reference.

Adverse Drug Reactions

Until the time of approval, adverse drug reactions (ADRs; including laboratory abnormalities) occurred in 46 of 95 patients (48.4%) evaluated for safety in the Japanese phase 2 clinical study. Major ADRs were increased AST in 13 patients (13.7%), increased ALT in 12 patients (12.6%), hypokalemia in 8 patients (8.4%), hyperlipidemia in 7 patients (7.4%), and hypertension in 4 patients (4.2%; unpublished data).

In phase 3 clinical studies conducted outside of Japan, ADRs (including laboratory abnormalities) occurred in 991 of 1333 patients (74.3%) evaluated for safety. The major ADRs were fatigue in 328 patients (24.6%), hot flash in 202 patients (15.2%), hypokalemia in 188 patients (14.1%), nausea in 179 patients (13.4%), peripheral edema in 160 patients (12.0%), hypertension in 125 patients (9.4%), constipation in 108 patients (8.1%), diarrhea in 101 patients (7.6%), vomiting in 92 patients (6.9%), dizziness in 81 patients (6.1%), increased AST in 69 patients (5.2%), and increased ALT in 68 patients (5.1%) [4,7].

Clinically Significant Adverse Drug Reactions

As cardiac failure and other serious cardiac disorders may occur (frequency unknown), patients are closely monitored. In the event of any abnormality, appropriate actions need to be taken, including discontinuation of treatment.

Fulminant hepatitis may occur (unknown frequency). Moreover, hepatic function disorder accompanied by increased AST (13.7%), increased ALT (12.6%), or increased bilirubin (2.1%) may occur and may result in hepatic failure (unpublished data). Thus, patients must be monitored closely using periodic liver function tests. In the event of any abnormality, appropriate

actions such as dose reduction or treatment interruption or discontinuation need to be taken.

Hypokalemia accompanied by symptoms such as convulsion or muscular weakness may occur, with some cases reportedly resulting in arrhythmia. Patients should be monitored closely by periodic measurements of serum electrolyte concentrations, including serum potassium. In the event of any abnormality, appropriate actions such as potassium supplementation or interruption of abiraterone treatment should be taken.

Thrombocytopenia may occur (unknown frequency), so patients must be closely monitored. In the event of any abnormality, appropriate actions including interruption of abiraterone treatment should be taken.

As rhabdomyolysis may occur, any muscular weakness, myalgia, increased creatine kinase (or creatine phosphokinase), and increased myoglobin in the blood or urine should be noted. In the event of any such symptoms, appropriate actions including discontinuation of abiraterone treatment should be taken.

Enzalutamide

Enzalutamide (Xtandi 40 mg capsules; Astellas Pharma, Tokyo, Japan) is a prostate cancer therapeutic agent. Usually, for adults, it is administered in a dose of 160 mg orally as enzalutamide, once daily. The efficacy and safety of enzalutamide have not been established in patients without concomitant surgical or medical castration. The precautions related to dosage and administration are as follows. It must be administered with care to the following patients: (1) patients with a current or past history of epilepsy or other convulsive disease (convulsive seizure may occur), and (2) patients predisposed to convulsive seizure (eg, patients complicated with cerebral injuries or stroke, who have such a history, or who are undergoing treatment with an agent that lowers the convulsive seizure threshold). Important precautions are as follows: (1) as an agent for endocrine therapy, enzalutamide should be used only in patients deemed indicated for enzalutamide treatment by a physician who is well versed and experienced in pharmacotherapies for cancer, and (2) as convulsive seizure may occur, patients undergoing treatment with enzalutamide should exercise caution when operating a motor vehicle or other machines associated with potential hazards.

Drug Interactions

Enzalutamide is metabolized mainly by the drug-metabolizing enzyme CYP2C8. Moreover, enzalutamide exhibits induction effects on CYP3A4, CYP2C9, CYP2C19, CYP2B6, uridine diphosphate-glucuronyltransferase, and P-glycoprotein. It exhibits inhibitory activity against P-glycoprotein, breast cancer-resistance protein, organic cation transporter 1, and organic anion transporter 3 [9]. Due to the long elimination half-life (4.7-8.4 days), enzalutamide may still induce or inhibit metabolic enzymes and transporters after completion of treatment.

In Japanese phase 1 and 2 clinical studies in CRPC patients, 31 of 47 patients who received enzalutamide (66.0%) developed ADRs. Major ADRs included hypertension (14.9%), constipation (14.9%), fatigue (12.8%), decreased appetite (12.8%), decreased weight (10.6%), and prolonged QT on

electrocardiograms (10.6%; unpublished data; as of the time of approval of the drug in March 2014.)

In phase 3 studies conducted outside of Japan in CRPC patients with prior docetaxel treatment, 554 of 800 patients who received enzalutamide (69.3%) developed ADRs. Major ADRs included fatigue (21.5%), nausea (20.1%), hot flash (15.0%), decreased appetite (12.6%), and asthenia (10.0%; as of the time of approval of the drug in March 2014) [5]

In an international phase 3 clinical trial in chemotherapy-naïve CRPC patients, 556 of 871 patients (including 28 Japanese) who received enzalutamide (65.0%) developed ADRs. Major ADRs included fatigue (25.3%), hot flash (13.4%), and nausea (13.3%; as of the time of amendment of precautions related to indications, October 2014) [6]

Clinically Significant Adverse Drug Reactions

Frequencies of the following ADRs are based on the tabulation of patients who received enzalutamide in the Japanese phase 1 and 2 clinical studies, non-Japanese phase 3 clinical studies, and an international phase 3 clinical trial.

As convulsive seizure (frequency 0.2%) such as convulsion and status epilepticus may occur, patients are monitored closely. In the event of any abnormality, treatment should be discontinued and appropriate actions taken.

Thrombocytopenia may occur (frequency unknown). As decreased platelets may occur, patients are monitored closely. In the event of any abnormality, treatment should be discontinued and other appropriate actions taken.

Definitions

The protocol treatment period is defined as the period of study drug (abiraterone or enzalutamide) administration as primary or secondary treatment.

The study period is defined as the period from the day of consent until the day of confirmation of the final outcome.

The investigator shall survey the outcome in patients after the protocol treatment is stopped until outcome confirmation or loss to follow-up.

Allocation to Study Drug

We are enrolling patients after obtaining written informed consent from each patient after providing them with written information on details of the study.

Patients are allocated to a treatment arm (abiraterone or enzalutamide treatment arm) in such a way that both arms are comparable in terms of (1) age (<70 vs ≥70 years) and (2) presence versus absence of metastases.

Study Schedule

Table 1 shows the study schedule. Tests listed in Table 1 are conducted on each patient before enrollment to assess whether the patient meets the inclusion criteria. Blood tests, including PSA, are conducted monthly. A quality-of-life survey (Functional Assessment of Cancer Therapy-Prostate [FACT-P]) is conducted every 3 months. Computed tomography (CT) bone scintigraphy is performed every 6 months.

Blood tests, including performance status and PSA, CT (chest and abdomen, plain), bone scintigraphy, and other tests are performed at crossover to the alternative treatment or when symptoms lead to suspicion of disease progression.

Table 1. Study schedule.

Test	Screening	Every month	Every 3 months	Every 6 months	At crossover or suspected disease progression	At study completion
Informed consent	+	–	–	–	–	–
Participant characteristics and underlying disease information	+	–	–	–	–	–
Eastern Cooperative Oncology Group performance status	+	+	–	–	+	–
Prostate-specific antigen	+	+	–	–	+	–
Hematology tests	+	+	–	–	+	–
Biochemical tests	+	+	–	–	+	–
Computed tomography (chest and abdomen, plain)	+	–	–	+	+	–
Bone scintigraphy	+	–	–	+	+	–
Prior treatment and concomitant therapy	+	–	–	–	–	–
Quality of life (Functional Assessment of Cancer Therapy-Prostate)	+	–	+	–	–	–
Adverse event	–	+	–	–	+	–
Information on discontinuation	–	–	–	–	+	–
Final outcome	–	–	–	–	–	+

Crossover of Study Drugs

On confirmation of PSA failure (deemed to have occurred when the PSA level reaches double the baseline level on 3 occasions, not necessarily consecutive, or progression is evident on imaging or a patient is considered to have trouble taking the study drug due to adverse events), the patient crosses over to receive the alternative study drug. Participants in this clinical study are those for whom docetaxel is not considered to be indicated. Nevertheless, before a patient crosses over to receive the alternative study drug, we explain to the patient again about the appropriateness of docetaxel treatment and evaluate the appropriateness. Patients who are deemed indicated for docetaxel treatment at this point in time shall be considered a dropout and given docetaxel treatment.

Observations, Tests, and End Points

Before Treatment Initiation

Before a patient initiates treatment, we check their consent to participate, performance status, PSA, hematology tests, biochemical tests, CT (chest and abdomen, plain), bone scintigraphy, presence or absence of prior treatment, and quality of life.

Efficacy Evaluation

PSA is checked monthly. Plain CT of the chest and abdomen and bone scintigraphy are performed every 6 months. At treatment crossover (enzalutamide to abiraterone, abiraterone to enzalutamide) or a switch to another therapy, including best supportive care, or when symptoms indicate suspected progression of disease stage, we perform plain CT of the chest and abdomen and bone scintigraphy as well, so as to assess the effects of the prior treatment and to check for any new lesions.

The measurement of PSA or imaging of progression-free survival with respect to the primary treatment begins on the first day of the primary treatment. The measurement of overall PSA or imaging progression-free survival after crossover from the primary to secondary treatment also begins on the first day of primary treatment. The measurement of time to use of chemotherapy or best supportive care, or the overall survival, also begins on the first day of the primary treatment.

Safety Evaluation

Adverse Events

An adverse event is any event (abnormal clinical finding, subjective or objective symptom, or abnormal change in laboratory test value) occurring during the study after initiation of the study drug treatment, regardless of the relationship to the study drug.

We evaluate adverse events based on an abnormal finding, symptom, laboratory test value, or severity according to the CTCAE version 4.0 [8].

Serious Adverse Events

An adverse event is serious if the event is observed any time after initiation of the study drug treatment up to 30 days following treatment completion (or discontinuation) and (1) results in death, (2) is life-threatening, (3) requires

hospitalization or prolongation of hospitalization for treatment, (4) results in persistent or significant disability or incapacity, or (5) results in a congenital anomaly.

On the occurrence of a serious adverse event for which a causal relationship to the protocol treatment cannot be excluded, the investigator shall provide appropriate interventions or treatments, promptly (within 24 hours of awareness) complete the required information on a Serious Adverse Event Report in accordance with the procedure at the medical institution the investigator is affiliated with, and communicate the event to the study secretariat by facsimile.

Laboratory Tests

Hematology tests are white blood cell count, differential white blood cell counts, hemoglobin, and platelet count. Tests are conducted at baseline and once monthly thereafter.

Clinical chemistry tests are AST, ALT, alkaline phosphatase, total bilirubin, creatinine, albumin, sodium, potassium, chlorine, phosphorus, and calcium. Tests are conducted at baseline and once monthly thereafter.

Primary End Point

The primary end point is PSA response rates (percentages of patients with PSA level decreasing by $\geq 50\%$) to the primary treatment in the abiraterone and enzalutamide treatment arms.

Secondary End Point

Secondary end points are (1) PSA or imaging progression-free survival with the primary treatment in the abiraterone and enzalutamide treatment arms, (2) PSA response rate (percentage of patients with PSA level decreasing by $\geq 50\%$) with secondary treatment in the abiraterone and enzalutamide treatment arms, (3) overall PSA or imaging progression-free survival after crossover treatment with both abiraterone and enzalutamide, (4) time to use of chemotherapy or best supportive care, (5) overall survival, (6) comparison of quality of life as assessed by FACT-P, and (7) adverse events.

Ethical Considerations

Compliance Regulations

All researchers involved in this research study shall comply with the *Declaration of Helsinki* (seventh revision, October 2013 [10], as translated by the Japan Medical Association) and the *Ethical Guidelines for Medical and Health Research Involving Human Subjects* [11] (enforced on April 1, 2015 and partially revised on February 28, 2017) in the conduct of this research.

Informed Consent

The principal investigator or investigator shall fully inform each participant by written information to allow them to decide whether to participate in the study and shall obtain from each participant written informed consent to participate in the study based on their own free will.

On obtaining written informed consent, the principal investigator or investigator who informed the participant shall confirm whether the participant fully understood the contents of the written information before consenting. The principal investigator

or investigator shall fill in the date on which the information was provided and the date of confirmation of the participant's intent on the written informed consent form and affix their seal or signature to the form. Each participant shall provide consent after gaining a full understanding of the contents of the written information, and shall then affix their seal or signature to and date the form.

The principal investigator or investigator shall provide a copy of the sealed or signed written informed consent along with the written information to the participant who provided consent and shall properly retain the original of the written consent at their medical institution.

When a matter arises that concerns the individual's intent to participate in the study, the principal investigator or investigator shall amend the written information, inform the participant again using the revised written information, and obtain written informed consent from the individual to continue participation in the study based on their own free will.

In the event a participant in the study requests withdrawal of consent, the request is documented in a study participation withdrawal form. If possible, a consent withdrawal form should be prepared. The participant shall fill in the date of withdrawal of consent and affix their seal or signature to the consent withdrawal form, and the principal investigator or investigator shall fill in the date of verification and affix his or her seal or signature to the form. The principal investigator or investigator shall provide a copy of the sealed or signed consent withdrawal form to the individual who withdraws consent and shall retain the original at their medical institution.

Approval by Institutional Review Board or Ethics Committee

Before the study is underway, the protocol, written information for the patient, written informed consent form, and the justification to conduct the study must be submitted for review by a committee at each study site (such as an institutional review board or ethics committee pursuant to the regulations of the study site) and receive its approval.

Safeguard of Personal Information

All parties involved in this study shall strictly safeguard the personal information of participants pursuant to the Japanese Personal Information Protection Act. When providing case report forms or information on adverse events and other relevant data to a party outside of his or her own medical institution, the investigator shall pay due attention to safeguarding personal information by actions such as replacing the identities of the participants concerned with participant identification codes or enrollment numbers so that no third party can identify the individuals. A reference table should be prepared that links the enrollment numbers issued to each participant at the time of acquisition of consent to each of their fields of personal information (name and medical record number), to allow identification or collation, as necessary, of enrolled participants whose information has been anonymized. The reference table is retained under strict safeguard at each study site. When identifying or collating an enrolled participant, the enrollment number issued at enrollment is used. Similar measures are taken

to safeguard the personal information of participants when publishing results of this research.

Important Findings on Genetic Characteristics

We do not expect this research to yield any important findings on the genetic characteristics of participants that may be relevant to health or inherited by their offspring.

Compensation

In the event the conduct of this study causes any adverse events that result in health hazards to a participant, the investigator shall administer appropriate treatments and take the best possible actions, including other necessary measures. Furthermore, as the conduct of this study is covered by insurance, any health hazards will be handled within the scope of the Adverse Drug Reaction Relief System [12].

Remuneration or Financial Burden to Study Participants

This research does not provide any remuneration to or impose any financial burden on the study participants.

Disclosure of Participant Information and Handling of Inquiries from Participants

In the event a participant personally requests the disclosure of information that involves privacy issues, in principle, the researchers (the principal investigator, coordinator, and investigator) at the study site that enrolled the participant shall handle such a request.

Participants may submit general inquiries or file complaints related to privacy by postal mail or email to the first author.

Statistics

Analysis Sets

The full analysis set includes all enrolled patients, excluding those with any major protocol violations (did not provide consent or any major procedural violations).

The per-protocol set includes those participants in the full analysis set who receive the study treatment allocated according to the protocol, excluding those who do not meet any eligibility criteria, meet any exclusion criteria, or take any prohibited concomitant drugs or other agents.

In all efficacy evaluations, we use the full analysis set as the primary analysis set, with analyses of the per-protocol set performed for reference purposes. We use the per-protocol set for safety evaluations.

Efficacy Evaluation

Primary End Point

For the primary end point, we calculate the point estimate and Clopper-Pearson exact 80% CI of the PSA response rate with primary treatment among the full analysis set population in the abiraterone and enzalutamide treatment arms, respectively. We determine the 95% CI and perform Fisher exact test for reference purposes. Furthermore, we calculate the odds ratio and 95% CI for PSA response. We estimate the impacts of prognostic factors and treatment effects by multiple logistic regression analysis, and estimate odds ratios adjusted based on the regression

coefficient of a multiple logistic regression analysis and its 95% CI. We use adjustment factors for allocation and any patient characteristics distributed unevenly between arms (with $P \leq .2$ as a guide) as influencing factors.

Secondary End Points

For PSA or imaging progression-free survival with primary treatment in the abiraterone and enzalutamide treatment arms, we determine the estimated survival curve among the full analysis set population in each arm by the Kaplan-Meier method. Under certain circumstances, we perform a similar analysis on the per-protocol set population. In such cases, we use the Greenwood formula to calculate the 95% CI and determine median survival, 1-year survival rate, and respective CIs. In addition, we use the Cox proportional hazard model to estimate the impacts of prognostic factors and treatment effects. We determine the estimated hazard ratio and its 95% CI based on the regression coefficient of the Cox proportional hazard model. We use adjustment factors for allocation and any participant characteristics that were distributed unevenly between arms (with $P \leq .2$ as a guide) as prognostic factors.

For PSA response rates with secondary treatment in the abiraterone and enzalutamide treatment arms, we determine rates by performing an analysis similar to that used to determine PSA response rates with the primary treatment among the full analysis set population in the abiraterone and enzalutamide treatment arms.

For overall PSA or imaging progression-free survival after crossover of the 2 treatment arms (abiraterone and enzalutamide), we determine survival by performing an analysis similar to that used to determine the PSA or imaging progression-free survival with the primary treatment among the full analysis set population in the abiraterone and enzalutamide treatment arms.

For time to initiation of chemotherapy or best supportive care, we calculate medians and interquartile ranges among the full analysis set population in the abiraterone and enzalutamide treatment arms and perform comparative analysis by the Wilcoxon test.

We determine overall survival by performing an analysis similar to that used to determine the PSA or imaging progression-free survival with the primary treatment among the full analysis set population in the abiraterone and enzalutamide treatment arms.

For comparison of quality of life as measured by FACT-P, we calculate medians and interquartile ranges among the full analysis set population in the abiraterone and enzalutamide treatment arms and perform a comparative analysis by the Wilcoxon test.

We tabulate adverse events in each arm and compare the severity and frequency of adverse events between arms.

Target Sample Size

Our target sample size is 50 participants ($n=25$ per arm). With no crossover treatment regimen consisting of abiraterone and enzalutamide, as first-line plus second-line treatment, available in Japan, we plan to conduct a pilot parallel-arm study in this

research. As such, the primary end point selected is the proportion of participants with a PSA response 50% or greater with first-line treatment. In studies to date, the PSA response with abiraterone as prior treatment was 78% in the PREVAIL study [6] investigating abiraterone as first-line treatment and enzalutamide as second-line treatment, while the PSA response was 62% in the COU-AA-302 study [7] investigating enzalutamide as first-line treatment and abiraterone as second-line treatment. Given its nature as a pilot study, the research must necessarily evaluate PSA responses in both arms in Japan, assuming that patient characteristics are evenly distributed. We thus consider CI of 80% (confidence coefficient .80) by the Clopper-Pearson exact method for the PSA response in each arm. With the expected PSA response of 70% in both arms and assuming a 1-sided interval width of 0.15%, the minimum sample size required is 21. Allowing for the potential that a few participants would become ineligible, we selected a sample size of 25 per arm, or a total of 50. The confidence coefficient of .80 is considered to correspond to a significance level of .10 on the 1-sided alternative hypothesis in a single arm. PSA response with second-line treatment was 17.6% for enzalutamide (first-line treatment) and abiraterone (second-line treatment) and 22.9% for abiraterone (first-line treatment) and enzalutamide (second-line treatment; Nadal et al [13]). With the expected PSA response with second-line treatment at 20% and assuming a sample size of 25, the 1-sided width of the 80% CI is 12.8%, which allows for estimation based on a CI width equivalent to that for the PSA response with first-line treatment.

Protocol Changes And Study Discontinuation or Completion

Protocol Changes

In the event of protocol changes becoming necessary during the study, the principal investigator shall decide what changes to make and promptly inform the investigator at each study site in writing about the changes and the reasons thereof. In cases of significant change to the protocol, the investigator shall report the change to the head of the medical institution and obtain an approval for the change, along with approval from the institutional review board or ethics committee.

Completion of Protocol

Once data lock is confirmed, we will consider the study to be complete. On receiving communication of the data lock from the data center, the principal investigator shall report on completion of the study to the investigator at each study site, who shall report the completion to the head of the medical institution and the ethics committee.

Discontinuation of Protocol

The rules to discontinue the entire study are as follows: (1) when the principal investigator determines after evaluating reports of study progress and study monitoring that completing the study is difficult due to reasons such as patient enrollment delays or frequent protocol deviations; (2) when serious safety or efficacy issues are judged to be associated with the study to justify its discontinuation based on new information that has become available after initiation of the study; and (3) when it is determined that safety issues are associated with the study or

that continuation of the study is not meaningful based on an evaluation of relevant information obtained from sources outside of this study, such as literature articles or conference presentations.

The procedure for deciding to discontinue the entire study are as follows. The principal investigator must request the ethics committee to conduct a review and accept its recommendations. Based on the recommendations, the principal investigator shall make a determination on the necessity to discontinue the entire study according to the rules provided in the preceding subsection. If the principal investigator disagrees with the recommendations, then the principal investigator shall report the reasons to the ethics committee.

After making a decision to discontinue the entire study, the principal investigator shall communicate with the investigators immediately about the reasons thereof and what actions to take. On receiving such a communication, investigators shall inform participants about discontinuation of the entire study and the reasons thereof, and shall immediately take appropriate actions.

Study Control

Monitoring

Monitors shall make sure that the human rights, safety, and welfare of participants are protected and that this study is conducted in compliance with the most up-to-date protocol and standard operating procedures. In addition, monitors shall access source documents and other study-related records directly to confirm that the data and other information reported by the principal investigator or investigators are accurate and complete.

Monitoring Methods

The data center shall perform monitoring centrally and periodically. In central monitoring, the case report forms collected and other data reported are checked to make sure that the study is conducted in a safe manner and in accordance with the protocol. Monitoring results are to be submitted to the principal investigator and ethics committees.

Deviations From Per-Protocol Treatments

The principal investigator or investigator may deviate from the protocol for this study if such deviation is medically unavoidable so as to avoid immediate hazard to a participant. In such a case, the principal investigator or investigator shall report the deviation and the reasons thereof to the ethics committee through the head of his or her institution as soon as possible. Moreover, the principal investigator or investigator shall document all deviations from the protocol for this study, regardless of the reasons.

Audits

No audits are planned in this study.

Retention of Source Documents and Other Records

Scope of Source Documents

The term source document in the study refers to any of the following: (1) records pertaining to participant consent and information provision; and (2) medical records, laboratory test data, imaging study films, and other records on which case

report form data are based; data saved in electronic medical records are also considered source documents.

Retention of Records by Participating Medical Institutions

The principal investigator shall retain the following study-related records for 5 years from the date of the final report or 3 years from the date of the final publication of the study results, whichever is later: (1) source documents; (2) informed consent forms and other documents related to this study or copies thereof that have been prepared by the personnel of a participating medical institution; (3) protocol (the latest version), documents pertaining to study review obtained from the institutional review board, and other documents obtained during the conduct of the study; and (4) other documents generated in the work related to the study.

Disposal of Records

Records will be disposed of according to the methods and procedures for retention and disposal established by the institution with which the researcher is affiliated, with consideration given to methods such as anonymization.

Information Entries in Case Report Forms and Their Submission

The investigators and others taking part in this study shall prepare case report forms in accordance with the *Guide on Filling Out Case Report Forms* (internal document) and submit the prepared case report forms to the data center by postal mail or in person. Investigators and other taking part shall prepare and retain a copy of each case report form before its submission.

Study Period

The study runs from December 2014 to December 2023. The patient enrollment period is September 2014 to December 2020.

Data Publication

The principal investigator has registered this study with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000022102) before beginning the study and shall register the end-of-study results on the same registry after study completion. Furthermore, the principal investigator shall publish the results in a conference presentation or a thesis promptly after completion of the study. Author names and their order shall be approved by the principal investigator and the protocol author before publication of the results in any conference presentation or journal submission.

Party Responsible for Costs of Study (Source of Funding)

As this study is supported by the research fund of the Department of Urology, Wakayama Medical University, Wakayama, Japan, there are no conflicts of interest.

Results

Recruitment started in May 2016, and 13 patients have been recruited so far. We expect to complete enrollment by December 2020.

Discussion

In terms of sequential therapy of novel hormonal preparations (abiraterone and enzalutamide), clinical outcomes of enzalutamide following abiraterone [14,15] or abiraterone following enzalutamide [16,17] have been reported. However, these were rather small-scale retrospective studies and, to our knowledge, no randomized trials comparing these sequential therapies have been reported.

Recently, cross-resistance between abiraterone and enzalutamide has been an issue of some focus. The most well-known mechanism of resistance is AR-V7, which is an androgen receptor splicing variant [18]. Patients expressing AR-V7 showed lower response rates and poor prognosis when treated with abiraterone as well as enzalutamide. In fact, the response

rate to the second drug is reportedly lower than that to first therapy in sequential therapies [14-17]. Urologists thus tend to prefer docetaxel over sequential therapies using 2 hormonal preparations after the progression of the first hormonal preparation. From that perspective, our clinical trial is rather out of fashion. Nevertheless, we assume that many patients are forced by necessity to undergo sequential hormonal therapy in the actual clinical setting, since most such patients cannot receive chemotherapeutic agents due to old age or poor performance status. This is why we are undertaking this randomized clinical trial comparing abiraterone versus enzalutamide. We are trying to identify which drug is most suitable for the initial hormonal therapy (in terms of not only antitumor effects, but also adverse events and quality of life) among CRPC patients who do not meet the indications for docetaxel therapy.

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Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CTCAE: Common Terminology Criteria for Adverse Events
CRPC: castration-resistant prostate cancer
CT: computed tomography
CYP: cytochrome P450
FACT-P: Functional Assessment of Cancer Therapy-Prostate
PSA: prostate-specific antigen

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Protocol

Community Volunteer Support for Families With Young Children: Protocol for the Volunteer Family Connect Randomized Controlled Trial

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Abstract

Background: Use of community volunteers to support vulnerable families is a widely employed strategy with a long history. However, there has been minimal formal scientific investigation into the effectiveness of volunteer home visiting programs for families. There is also a need for research examining whether volunteer home visiting leads to improved outcomes for volunteers.

Objective: The objective of this paper is to describe the research protocol for a pragmatic randomized controlled trial (RCT) of the Volunteer Family Connect intervention, a volunteer home visiting program designed to support families of young children who experience social isolation or a lack of parenting confidence and skills. The project is being conducted in partnership with 3 leading not-for-profit organizations, designed to contribute to the body of evidence that informs decisions about appropriate family support services according to the level of need. It is the first study to examine outcomes for both the families and the volunteers who deliver the service.

Methods: The RCT is being conducted in 7 sites across Australia. We aim to recruit 300 families to the study: 150 control (services as usual) and 150 intervention (services as usual + volunteer home visiting) families. Intervention families will receive the service for 3-12 months according to their needs, and all participants will complete 6 data collection points over 15 months. A minimum of 80 volunteers will also be recruited, along with a matched community comparison group. The volunteers will complete 3 data collection points over 12 months. Primary outcomes include community connectedness and parenting competence. Secondary outcomes include parent physical and mental health; general parent well-being; parent empowerment; the child-parent relationship; sustainability of family routines; child immunization; child nutrition or breastfeeding; number of accidental injury reports; and volunteer health, well-being, and community connectedness.

Results: This effectiveness trial was funded in 2016, and we aim to complete data collection by the end of 2018. The first results are expected to be submitted early in 2019.

Conclusions: There is a need to rigorously assess volunteer home visiting and whether it has a unique and important role on the service landscape, complementary to professional services. This research is the first trial of a volunteer home visiting program to be conducted in Australia and one of the largest of its kind worldwide.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12616000396426; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370304> (Archived by WebCite at <http://www.webcitation.org/70q42fU7V>)

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KEYWORDS

randomized controlled trial; volunteer home visiting; families; support services

Introduction

Volunteer home visiting is a widely adopted community-based approach to support families, linking vulnerable and isolated families to trained volunteers from their local communities who have experience in parenting or caring for children. Volunteer home visiting programs can take different forms, with many seeking to support families by helping them strengthen their social and community networks, providing families with connections to appropriate local health, welfare, and education services and support information [1]. Volunteers may also work with parents to increase their parenting confidence, encourage positive parent-child relationships, share local knowledge, and foster a sense of belonging and community resilience [2]. Bronfenbrenner's bioecological model [3,4] emphasizes that building resilience in both parents and the communities in which they live is critical to achieving family physical, mental, and social well-being. Bronfenbrenner described a complex and dynamic web of relationships that exist between children, their families, the settings in which children participate, and the wider community. Child health and well-being outcomes are strongly influenced by the many social and environmental contexts that operate within a child's life. Factors across contextual layers accumulate to increase a child's or a parent's resilience or risk factors. This requires the development of social infrastructure to support the growth of inclusion networks and opportunities for meaningful civic participation [1].

While previous research has demonstrated that a sense of belonging and inclusion in the local community context is fundamental to health and well-being [5,6], there are increasing reports of isolation, segregation, and nonparticipation in response to changing community environments [7]. A sense of isolation is particularly evident in research examining the social inclusion of families in need of additional supports, such as new arrivals to a country [8], those with demanding care responsibilities [9,10], and those who experience cognitive limitations or mental health challenges [11].

There is an argument for volunteer home visiting having a unique and necessary place on the landscape of services available to families because of the following reasons: (1) It fills the service gap for families whose circumstances do not meet the eligibility criteria for targeted or sustained professional home visiting services and yet need more support than is available from universal primary health and community services

and (2) It is designed to break down potential barriers to service access, such as language, transport, or cultural barriers. Another unique feature of the volunteer home visiting model is that there are two groups within the community who, according to emerging evidence, potentially benefit—the families who receive the service and the volunteers who deliver the service [12-14].

Despite its long history and critical role within Australian service systems, there has been relatively little formal scientific investigation into the effectiveness of volunteer home visiting programs. Comprehensive reviews criticize the available evidence for volunteer home visiting as being largely characterized by research with methodological limitations that is focused on program satisfaction and experiences of participation rather than outcomes [15,1]. Nonetheless, findings from the existing literature suggest there is a role for volunteer home visiting in supporting families with vulnerabilities. International research indicates that this service model may provide an acceptable vehicle for the distribution of health and parenting information [16] and improve family social support networks, both in terms of social capital as well as family social connectedness [17,18]. It has also been shown that volunteer support can contribute to improved outcomes relating to parental emotional well-being [19,20], parental sense of competence [21-23], parent-child relationships [24], and parenting behaviors and skills [25]. There is particularly strong evidence that peer support can play a key role in promoting increased rates of breastfeeding and child immunization [26-28]. There is also potential for volunteer home visiting models to play an important support role in the care plans of those with chronic health conditions [29]. It should be noted, however, that community volunteers may not have a marked impact on clinical outcomes, which may be more appropriately addressed by professional services [30], and volunteer support needs to be provided within the context of well-developed guidance and supervision [31,32]. The small number of studies that examine volunteering in the context of family support programs suggest that volunteers experience positive outcomes such as increased knowledge and skills, a stronger sense of social cohesion, reduced loneliness and isolation, and an improved sense of purpose and confidence [11].

The aim of this research is to rigorously explore the effectiveness of the Volunteer Family Connect program (ACTRN12616000396426), a volunteering home visiting program collaboratively designed by a consortium of researchers

and service providers in Australia to support families of young children who are vulnerable because they experience social isolation or a lack of parenting confidence and skills. Volunteer Family Connect is a community-based strategy that aims to improve the well-being, social connection, and parenting of vulnerable families with young children and the well-being and social connection of community members who volunteer. The results can be used to inform public policy on this issue.

Methods

Study Design

A pragmatic randomized trial design is being undertaken to provide high-quality evidence to assess the impact of the Volunteer Family Connect program. Pragmatic trials are a rigorous method for assessing effectiveness, that is, the degree of beneficial effect of intervention programs in real-world conditions, answering the question “Does this intervention work under usual conditions?” [30]. In keeping with the “real-world” conditions for a pragmatic randomized trial, in this study, we performed the following:

- We recruited the full range of families referred to the volunteer home visiting programs of the partner organizations through usual referral processes, with no changes to service inclusion and exclusion criteria.

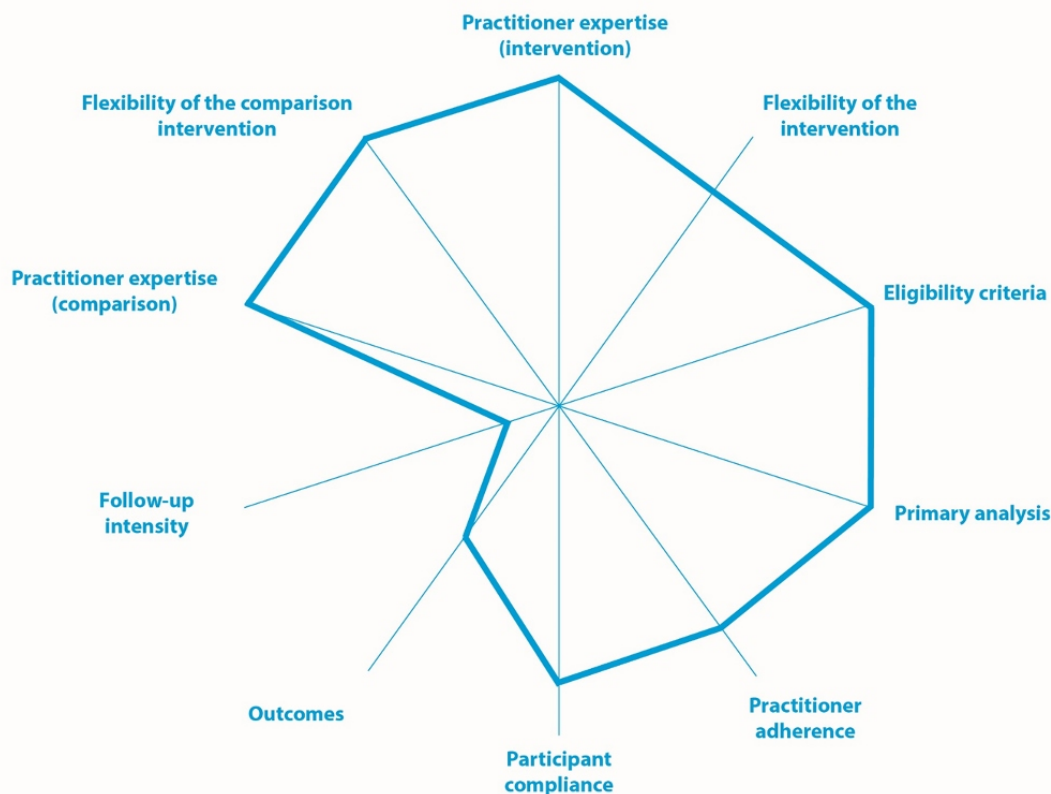
- We compared the volunteer home visiting program with other usual care support services, such as group activities and referral to other agencies.
- We tested real-world implementation of the volunteer home visiting program by our service partners with their current volunteer providers using guidelines to support quality service provision, but acknowledging that there are variations in practice, while rigorously assessing outcomes using standardized measurement tools.

The design of the study was supported using the PRagmatic Explanatory Continuum Indicator Summary (PRECIS) tool [33], which assesses the varying degrees of pragmatic (effectiveness) and explanatory (efficacy) trial approaches. Wider webs represent more pragmatic trials: narrow webs represent more explanatory trials. The PRECIS web for the current trial is depicted in Figure 1. Rating of the Volunteer Family Connect trial on the PRECIS tool was completed collaboratively by the research team. All senior members of the research team gathered in a face-to-face meeting and discussed the project as it is reflected in scores on the PRECIS tool until consensus was achieved.

Primary Research Question

Is a volunteer home visiting service intervention effective in improving the parenting competence and community connectedness of vulnerable families with young children compared with families who receive usual care services in the community?

Figure 1. Using the PRagmatic Explanatory Continuum Indicator Summary tool to describe the Volunteer Family Connect randomized controlled trial.



Hypothesis

Families receiving a volunteer home visiting service intervention will have significantly better family outcomes at 15 months post program entry (higher sense of parenting competence and stronger community support networks) than those allocated to continue to receive usual community-based support services.

Secondary Research Questions

1. Do differences exist in the patterns of parent health, well-being, and empowerment and the sustainability of family routines over time between those who receive the Volunteer Family Connect program and those in the services as usual control group?
2. Does volunteer home visiting lead to differing outcomes for children aged 0-5 years in intervention families compared with those in control group families on measures of immunization, breastfeeding duration, nutrition, and accidental injury?
3. Do different patterns of outcomes for intervention families depend on the location (ie, availability and accessibility of health, welfare, and early childhood services in the local area) and the duration of the program (ranging from 3 to 12 months)?
4. Does volunteering on the Volunteer Family Connect program lead to differing outcomes on measures of well-being, health, community connectedness, and self-efficacy for volunteers over time compared with a matched community comparison group?

Participants

Eligibility Criteria

Eligible families will be those who meet the following criteria: (1) families having one or more children in the 0-5 age range; (2) families at risk of geographic or social isolation (eg, separated from usual support networks due to immigration); (3) parents seeking to develop confidence and increase their parenting knowledge and skills; (4) families residing in the specified service area; and (5) families unable to resource or access other support services (eg, due to financial hardship). Language translation services have been secured so that families with a first language other than English will not be excluded from participating in the research.

Families will be ineligible for the study if any of the following conditions apply: (1) there is active abuse or domestic violence within the family; (2) there is unmanaged mental illness within the family; (3) substance abuse is an issue within the family; (4) the family is living in an environment unsafe for the volunteer to visit; and (5) the family is under child protection orders or there are unsettled parenting arrangements. Families referred for volunteer home visiting will be assessed for eligibility by the local Volunteer Family Connect program coordinator according to the usual practice, and referrals will be made to other services within the community if the family is ineligible.

All current volunteers within the Volunteer Family Connect program will be invited to participate in the study. It is not possible to examine outcomes for volunteers employing a randomized controlled trial (RCT) design because this would halve the number of volunteers available and significantly impact program implementation. Instead, a community comparison sample will be recruited that will be matched on age, gender, education and employment levels, and geographical location.

Recruitment

Family participants will largely be identified through the Volunteer Family Connect usual service referral networks, which include child and family health nurses, general practitioners, or family support workers. The Volunteer Family Connect program is advertised within the community, and parents are welcome to self-refer to the program. If eligible for the program, families will be invited to speak to a member of the research team and, if interested, informed consent for the research will be secured. The family will then be randomly allocated by the research manager using computer-generated random numbers to receive either the volunteer home visiting program in addition to usual care services (Intervention group = Volunteer Family Connect + usual care services) or the usual care services only (Control group = usual care services).

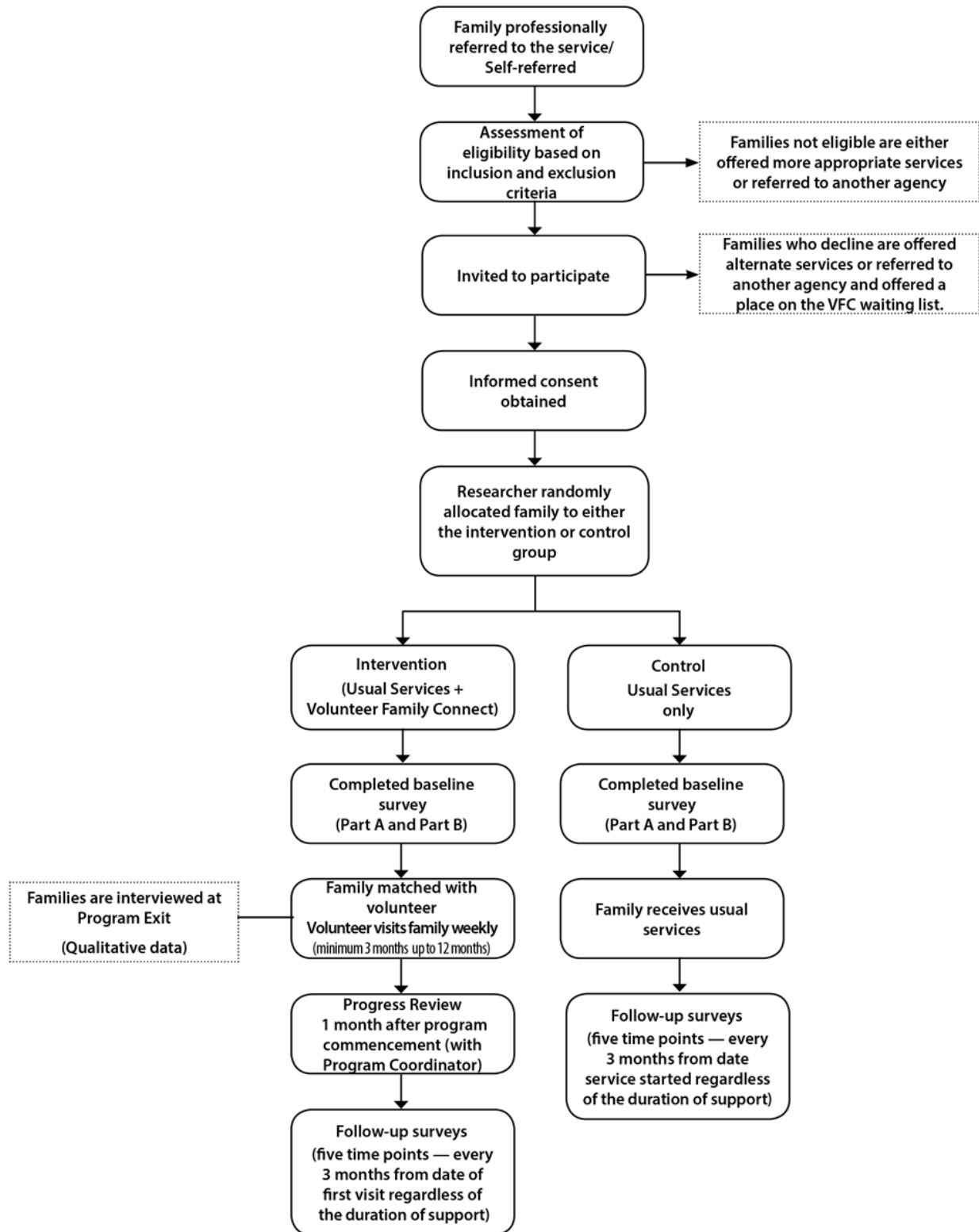
The procedure used to recruit and allocate families is summarized in [Figure 2](#).

An invitation will be extended to all volunteers currently involved with the 7 participating sites to participate in the research. The matched community comparison sample will be recruited via one of the following two strategies: (1) volunteers will be asked to pass on an invitation to participate in the research to nonvolunteering acquaintances in their local networks and (2) the research will be advertised through Facebook, targeting the local areas in which the Volunteer Family Connect program is being trialed.

Sample Size

We aim to recruit 300 families to the study, 150 to the intervention group (Volunteer Family Connect + usual services) and 150 families to the control group (usual services). Recruitment of 150 families per group has been undertaken based on what is feasible given current caseloads in the participating sites and also so that, allowing for attrition, data analysis can be conducted with a final sample size of 100 families per group. A sample size of 100 families per group has power of .80 at the 95% level to detect effect sizes (ESs) of .5 or larger for the PSCS Satisfaction subscale (significant differences detected with minimum $n=16$ per group) and the Client Enablement Index (significant differences detected with minimum $n=7$ per group) based on pilot study findings and a previous trial of nurse home visiting conducted by one of the chief investigators on this study [34].

Figure 2. Participant flow diagram.



The families will participate in data collection for a period of 15 months. Strategies have been put in place to support and encourage the retention of participants, including asking all participating parents to provide the name and phone number of a relative or friend who can be contacted by the researchers if we struggle to reach them; providing families with the contact details of the research team and asking them to advise us if their contact details change; providing each family with an Aus \$20 gift voucher for a popular grocery store chain at each data

collection point and sending thank you notes; and employing project offices who have strengths in the building of rapport with families. The decision to employ these strategies was primarily based on the positive experiences of the research team in the previous research projects [34,35].

A total of 80 volunteers and 80 comparison group members will be recruited to the study, reflecting current volunteer numbers.

Participant Timeline

Data collection spans a 15-month period so that there is at least one data collection point post family exit from the Volunteer Family Connect program (families receive the program for 3-12 months depending on their support needs). Volunteer outcomes will be measured over a 12-month period at 6-month intervals.

Intervention

Development

The Volunteer Family Connect program was developed in conjunction with 3 leading not-for-profit organizations, all involved in coordinating volunteer home visiting programs in the eastern states of Australia: The Benevolent Society; Good Beginnings Australia (later subsumed into Save the Children Australia); and Karitane. An executive member from each partner organization along with the research leaders met every 6 weeks for approximately 5 years. Collaboratively, a “best practice” model of volunteer home visiting was developed based on a shared theory of change, the strengths of the existing programs, practice wisdom, and existing research evidence. The program was manualized, and practice tools were created such as fidelity checklists, family progress tools, and volunteer training schedules. The Volunteer Family Connect program is currently being implemented with fidelity in 7 trial sites across 4 states (New South Wales, Queensland, Tasmania, and Victoria) including city, suburban, and rural settings.

Preparation for the trial has also involved extensive and ongoing consultation and support for program coordinators and provision of training across all levels of the partner organizations (including volunteers) to increase the understanding of, and support for, the conduct of an RCT.

Pilot Study

Early preparatory work included a pilot and feasibility study. The methods and results of this small study comparing Volunteer Family Connect families with supported playgroup parents over a 6-month period have been reported elsewhere [36]. Family outcome measurement tools were piloted for face validity and ease of use, and the project survey instrument was refined in line with parent feedback and researcher experience of administration. The range of “usual care” programs and services (ie, programs and services available to all members of the community) were identified, and the processes for family recruitment to the trial and randomization were established and tested.

Delivery in the Trial

The families assigned to the intervention group will receive the Volunteer Family Connect program delivered by a volunteer associated with one of the partner organizations in the 7 trial sites. The Volunteer Family Connect program comprises the core components described below.

1. Program Coordinators: Each site has an employed program coordinator with tertiary qualifications in social work or a

related field. The program coordinators are responsible for recruiting and training the volunteers, establishing referral networks, matching volunteers with families, providing regular supervision to volunteers, conducting intake and progress interviews with families, and referring families to other services within the community.

2. Trained volunteers: All community volunteers participate in a minimum of 30 hours of training before being matched with a family and must participate in two additional capacity-building sessions each year. Examples of core training modules include “a strengths-based approach to working with families,” “reflection on personal values and attitudes,” “boundaries and self-care,” “child development,” and “community resources.” The topics for ongoing capacity-building sessions are decided by the program coordinator depending on family needs at the time. For example, if there are high numbers of families who have infants, topics like “breastfeeding” or “sleeping and settling” may be chosen. All volunteers undergo a background check.
3. Matching: Program coordinators match families with a volunteer, guided by the needs of the family but limited by the pool of volunteers available.
4. Home visits: Volunteers visit the family for approximately 2 hours every week. What happens during visits will depend on the needs of the family. Volunteers are encouraged to support families to connect with other services and facilities within the community (eg, attend local playgroups, visit the child and family health center, go to the park, etc) and link them with information as needed. Volunteers are also expected to model positive interactions with the children and encourage the parents in their personal and family goals. Volunteers do not do cooking or housework tasks unless it is with the parent as part of helping them to learn how to do these tasks, and they do not provide child-minding or child care such as changing nappies or bathing children. Volunteers complete checklists following each home visit, detailing the activities and topics of discussion with the family and whether information was provided to the family or the family linked with another service in the community. The collated data are used as a measure of program fidelity and provide ongoing quality feedback to the service partner organizations.
5. Exit interviews: The duration of the service will be a minimum of 3 months and a maximum of 12 months. When the family, volunteer, and program coordinator agree that the family has met their goals, the family is exited from the program and referred to other services by the program coordinator as appropriate.

Control Group, Services as Usual

Neither intervention nor control group families are limited in the extent to which they are able to access other services within the community. It is anticipated that most families will access a range of early childhood health and education services. Family use of other services will be documented in the research, based on parent self-report, and explored as a variable in analysis.

Table 1. Outcome measures.

Outcomes and Construct Measured	Data Collection Schedule					Instrument	
	Enrollment (Baseline)	Months					
		3	6	9	12	15	
Primary Outcomes							
Community connectedness	✓	✓	✓	✓	✓	✓	Community Connectedness Scale [37]; Social Provisions Scale [38].
Parenting competence	✓	✓	✓	✓	✓	✓	Parenting Sense of Competence Scale [39].
Secondary Outcomes							
Parent							
Parent physical and mental health	✓	✓	✓	✓	✓	✓	SF-12 ^a [40].
General parent well-being	✓	✓	✓	✓	✓	✓	The Outcome Rating Scale [41].
Parent empowerment	✓	✓	✓	✓	✓	✓	Modified Patient Enablement Instrument [42].
Child-parent relationship	✓	✓	✓	✓	✓	✓	Parental questionnaire (questions from the Canadian National Survey of Parents of Young Children) [43].
Child							
Immunization	✓	✓	✓	✓	✓	✓	Child Personal Health Record.
Nutrition or breastfeeding	✓	✓	✓	✓	✓	✓	Parental questionnaire-Breastfeeding questions from the New South Wales Child Health Survey (CHS; CHS items CBF ^b 1, CBF2, and CBF13) [44].
Accidental injury	✓	✓	✓	✓	✓	✓	Parental questionnaire: "In the last 3 months, did your children get injured at home? If yes, did the injury require medical attention (eg, your child needed to go to a hospital emergency room or general physician for medical attention)?"
Family							
Sustainability of family routines	✓	✓	✓	✓	✓	✓	Ecocultural Family Interview [45].
Service use							
Satisfaction with the VFC ^c program and other services being accessed	✓	✓	✓	✓	✓	✓	Checklist of local community services. Modified Patient Satisfaction Questionnaire Short Form [46]. Rating of Expectations identified at program entry on a 10-point Likert Scale (<i>intervention only</i>). Semistructured interview at program exit to reflect on experience of program participation (<i>intervention only</i>).
Volunteer							
Volunteer mental and physical health	✓		✓		✓		SF-12 [40].
Guidance, reassurance of worth, social integration, nurturance, reliable alliances, and attachment	✓		✓		✓		Social Provisions Scale [38].
Social connectedness and knowledge of community resources	✓		✓		✓		Community Connectedness Scale [37].
Confidence or belief in meaningfulness of volunteer participation	✓		✓		✓		Community Service Self-Efficacy Scale [47,48].
Motivational drives of volunteers	✓		✓		✓		Volunteer Motivation Inventory [49].

Outcomes and Construct Measured	Data Collection Schedule					Instrument	
	Enrollment (Baseline)	Months					
		3	6	9	12	15	
Process							
Volunteer activities or Experience of program participation		✓ ^d	✓ ^d	✓ ^d	✓ ^d	✓ ^d	Visit record sheet checklist is completed at every visit. Volunteer visits weekly for a minimum of 3 mo and a maximum of 12 mo. Volunteer completes a checklist of topics and activities covered during the visit and qualitative questions, including volunteer perception of the impact of the program on the family.

^aSF-12: 12-Item Short Form Health Survey.

^bCBF: child breastfeeding.

^cVFC: Volunteer Family Connect.

^dCollected weekly for the duration of the intervention.

Outcomes

In keeping with the processes of a pragmatic randomized trial [37], primary and secondary outcomes were chosen in collaboration with the partner organizations and in consultation with volunteers and families, based on their perceptions of the expected benefits of volunteer home visiting and the importance of the outcome to the families and their volunteers. Discussions on appropriate outcomes were conducted in monthly steering committee meetings with senior representatives from all partner organizations, in focus groups with volunteers held in every participating site, and in focus groups with families conducted within the Sydney-based sites. Wherever possible, tools previously demonstrated to have power to show significant differences between the intervention and comparison groups with a minimum of 100 participants per group were selected; however, many of the expected outcomes have not previously been measured in home visiting studies. With the exception of the home visiting program satisfaction scale (intervention group only), measures are identical for both family intervention and comparison groups. Measures are identical for the volunteer group and the matched community comparison group. In addition, program process data will be collected. The measures are presented in Table 1.

Allocation

Most families will be allocated on an individual basis using computer-generated randomizing, giving them an equal chance of being allocated to the intervention or the control group. If more families are recruited than the number of available volunteers, randomization will be proportional using computer-generated randomizing (eg, if there are five available volunteers and seven recruited families, five of the seven families will be randomly allocated to the intervention group and two to the usual care group).

Family group random allocation will be the responsibility of the research program manager who will be blind to any details about the family when making this allocation. Once the allocation is determined, the program manager will notify the appropriate program coordinator. It will not be possible to blind the research staff responsible for data collection: families will

know their allocation and are likely to disclose this to the researchers during data collection. While data collection is not blind, data analysis will be blind, completed by team members who have not been involved in data collection.

Data Collection, Management, and Security

Interviewers are trained in the standard administration of the instruments and handling of distressed parents or volunteers. The research team meets at least monthly to review interview techniques and ensure consistency of administration. All data are checked to ensure accuracy and consistency of data entry.

Family participants will complete a survey every 3 months for 15 months, commencing at recruitment and continuing until 15 months post their own recruitment date. The baseline and follow-up surveys will be collected by a research assistant (at the home of the participant or over the phone) or self-completed by participants if preferred. Surveys can be completed on a paper form or a word document sent via email, or they can be Web based using Qualtrics software (Qualtrics, Provo, UT). The Web-based version of the survey has been tested for usability and technical issues in one of the study sites and will eventually be rolled out to all sites. Previous research suggests that offering multiple survey response modes allows participants to choose what is most convenient for them, with little negative impact on data quality [50]. The use of iPads and Web-based survey software has been shown in the previous research to increase efficiency and reliability and to reduce data entry errors [51-53]. All data collected via paper or emailed word documents will be entered into the Web-based survey by a research assistant. Data will be stored in a password-protected Qualtrics database and backed up to a password-protected folder on a server. Only members of the research team will have access to the data.

The Web-based survey will be administered in two sections. Section A includes prefilled items (eg, demographic questions, breastfeeding status, service expectations) for the participant to update (if applicable), and Section B contains all other items. Section A requires a link to be manually generated for each participant at each time point. Section B uses a generic link to the respective time point. For participants self-completing, both

Section A and Section B links will be manually emailed by research assistants in each site and reminders (emails, text messages, or phone calls) will be sent weekly until the survey is completed or for 6 weeks post the due date for the survey. Both sections require the participant to enter a unique identifying number at the start of the survey. Where duplicate entries occur, the earliest completed response will be retained.

Items will always be presented in the same order, and adaptive questioning will be used to only display relevant questions to participants. Dependent on adaptive questioning, Section A has a minimum of twelve pages and a maximum of forty-five pages, with a maximum of eight questions per page. Dependent on adaptive questioning, Section B has a minimum of forty-three pages and a maximum of seventy-eight pages, with a maximum of six questions per page. Multiple-choice questions use forced choice validation, with an option of “refused” on all questions. Open-field responses use requested response validation, with a prompt appearing before the survey can be progressed to the next page. A back button will be available to the respondents; however, there is no provision to review the completed survey before submission.

Volunteers and comparison group members can opt to complete their surveys over the telephone with a research assistant who enters their response into the Web-based survey using an iPad, independently using a paper survey that is mailed to them, or Web based using Qualtrics.

All data are stored on password-protected computers at Macquarie University and at Western Sydney University, to which only the research team has access. Data are de-identified during data entry, at which time all names are replaced with participant numbers. Data are stored in accordance with the requirements of the Australian National Health and Medical Research Council and the Privacy Act 1988.

Data Analysis

Quantitative Analysis

Primary and secondary outcomes will be extracted and analyses conducted using SPSS Version 25.0. Analysis will be completed both on an intention-to-treat and a per-protocol basis. Families will be considered to have received the scheduled dose if they receive visits from the volunteer for at least 3 months with no gap between visits of more than 2 weeks. Volunteer outcomes will be analyzed using cross-sectional comparative analysis. Participant demographic data will be analyzed using basic descriptive statistics. Prior to the analysis of outcome measures, data will be assessed for outliers and normality. Scale variables will be analyzed using independent *t* test or analysis of variance or their nonparametric counterparts (eg, Mann–Whitney U test) if appropriate. Mixed modeling will be completed on the primary and secondary family outcomes to assess the effect of the intervention over time while adjusting for possible confounders. Categorical variables will be analyzed using odd ratios or chi-square analysis. For all analyses, two-tailed tests will be undertaken: findings with $\alpha < 0.05$ will be determined to be statistically significant. ESs will be calculated for all trends ($\alpha < 0.1$) and statistically significant findings; (ES=0.5 [Cohen *d*]) will be considered clinically meaningful. Overall, the

program will be considered to have been effective if at least one of the primary outcomes is positive and the other is neutral.

Qualitative Analysis

The survey instruments include some open-ended questions. The qualitative data will be extracted into a text file for analysis and entered into NVivo (QSR International). Analysis of the open-ended responses will employ a thematic approach, with themes and relationships between themes identified and described. The first ten interviews will be dual-coded, followed by the development of a coding framework then independent coding with regular checks for inter-rater reliability. Analysis will initially focus on the family as a case and explore change in the family’s reported experience over time. It will then expand to compare themes across the families as a group to capture the collective experience.

Ethics

Ethics approval for the study was granted by the Macquarie University Human Research Ethics Committee (Reference number: 5201401144).

Data Availability

The data that support the findings of this study will be made publicly available at the conclusion of the research on request to the corresponding author RG.

Results

Seed funding for this project was provided by a private philanthropist, who went on to fund the effectiveness trial described here commencing in 2016. Data collection is currently underway and will be complete by the end of 2018. The first results are expected to be submitted for publication early in 2019.

Discussion

In this study, we aim to explore the effectiveness of a volunteer home visiting program designed to provide support to families with young children who might otherwise “fall between the cracks” because they are not eligible for intensive family support services but need more support than is available through universal primary services. The Volunteer Family Connect study will provide evidence of the outcomes for families based on the program logic of volunteer home visiting [1] and outcomes desired and valued by parents. This study assesses the effectiveness of volunteer home visiting on its own merits and contribution to the service landscape, rather than as a program equivalent to, or potential substitute for, professional services.

RCTs can be an uncomfortable methodological approach for not-for-profit organizations. Their employees are generally guided by an altruistic and empathic approach, rather than a rigidly scientific approach, and randomly denying support to someone they believe would benefit can be challenging. Time was spent with those delivering the program to discuss the ethical situation in the context of delivering the previously untested service that did not have evidence of effectiveness. The lengthy lead in time for this project was essential to secure

support for the research across all levels of the organizations, from CEOs and board members, through to program coordinators and volunteers. Some volunteers and program coordinators did not want to be involved, and the services have also experienced some difficulties with their referral networks, with some referrers ceasing to refer families during the research trial. Understanding these significant challenges for participating organizations and their ongoing commitment to ensure a rigorous research approach is commendable. Launching this research is an indication that within the not-for-profit sector, rigorous research is feasible. It does, however, need to be embedded within trusting relationships and will need many formal and informal conversations across all levels of the organization, which can take several years.

Future research will explore different modes of program delivery, including whether volunteer home visiting can be effectively delivered using technology such as telephone and videolinks. This work will complement the existing research exploring the role of technology in providing professional and other support services to those in rural and remote regions [31].

A strength of this study is that it is part of a comprehensive program of research that employs an ecological approach [4] guided by an understanding that the health and well-being of parents, the stability of families, the strength of social interactions, the safety of neighborhoods, and respect for cultural contexts are all equally important for achieving positive outcomes for children. In conjunction with the RCT of family outcomes are the following: (1) a matched comparison study on the benefits of volunteering; (2) a mixed-methods study of program implementation that explores program quality and fidelity; and (3) a social return on investment analysis. This RCT and the three additional studies will interlink and directly inform the analysis and interpretation of findings across the program of research. As a whole, this program of research has the potential to make a significant contribution to our understanding of the support and service needs of vulnerable families and the value of volunteering as a mechanism to mobilize and strengthen communities.

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Authors' Contributions

RG led the writing of this paper. EE and LK took primary responsibility for the design of the analysis plan. All authors made substantial contributions to the conception and design of the research and to the revision of the manuscript and have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ES: effect size

PRECIS: PRagmatic Explanatory Continuum Indicator Summary

RCT: randomized controlled trial

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Protocol

The Family Check-Up Online Program for Parents of Middle School Students: Protocol for a Randomized Controlled Trial

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Abstract

Background: Research has established that skillful family management during adolescence protects youth from a variety of mental health and behavioral problems. Interventions associated with this research have focused on parenting skills as the mediator that links early risk factors with a profile of later behavioral risk, including problem behavior, substance use, and school failure. Fortunately, positive changes in family management skills have been linked to meaningful improvements in adolescent behavior, and these improvements have been significant across a variety of cultural groups.

Objective: We describe the background, research design, and intervention components of an electronic health version of the Family Check-Up program that is targeting middle school children and is being evaluated in a randomized controlled trial for its usability, feasibility, and efficacy.

Methods: We used an iterative formative research process to develop an electronic health version of the Family Check-Up program. In our ongoing randomized controlled trial, eligible families are randomly assigned to 1 of 3 conditions: Family Check-Up Online-only (n≈100), Family Check-Up Online + Coach (n≈100), and a waitlist control condition (middle school as usual; n≈100). We are conducting assessments at baseline, 3 months following randomization (posttest), and at follow-ups scheduled for 6 months and 12 months.

Results: This randomized controlled trial project was funded in 2015. Participant recruitment was completed in spring 2018 and enrollment is ongoing. Follow-up assessments will be completed in 2019.

Conclusions: The innovative Family Check-Up Online program has the potential to help address many of the barriers that more traditional school-based behavioral mental health implementation strategies have yet to solve, including staffing and resources to implement family-centered support within schools.

Trial Registration: ClinicalTrials.gov NCT03060291; <https://clinicaltrials.gov/ct2/show/NCT03060291> (Archived by WebCite at <http://www.webcitation.org/70f8keeN4>)

Trial Registration: RR1-10.2196/11106

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KEYWORDS

family treatment; parent-child treatment; school mental health; internet intervention; eHealth intervention; prevention science; family relations; parent-child relations; school health services; mental health services; telehealth; preventive psychiatry; preventive health services

Introduction

Background

Although many young people make the transition to adolescence with only minor behavioral problems and school-related difficulties, a significant number of at-risk youth develop problem behaviors that are serious, that may last a lifetime, and that could impair later functioning. During the past decade, substance use has remained a serious public health concern, with 35% of eighth graders reporting having tried alcohol and associated increases in substance use during the adolescent years [1]. Early adolescence (ages 11-14 years) is a time of rapid biological and social transition. Interactions between parents and their child's middle school are significantly more formalized and less frequent than in elementary school [2]. As a result, parents tend to become less involved in their child's overall adjustment, which may subsequently lead to a variety of behavioral and social problems in high school. As a result, middle school is an ideal developmental period for family-centered prevention that targets reduction of problem behavior and substance use through teaching and supporting effective parenting skills.

Research during the past two decades has established that skillful family management, including applying positive parenting skills, setting limits, monitoring, and effectively solving problems, during adolescence protects youth from a variety of mental health and behavioral problems. Most family-centered intervention studies have focused on parenting skills as a direct target of intervention, guided by a theoretical model whereby parenting skills are the mediator that links early risk with a profile of later behavioral risk, including problem behavior, substance use, and school failure [3-6]. Fortunately, positive changes in parental family management skills have been linked to meaningful improvements in adolescent behavior across family cultures and ethnic groups [7,8]. Even among adolescents who exhibit risk, such as affiliation with deviant peers, improved family management skills by parents has been shown to decrease the growth of externalizing behavior during adolescence [9].

In this paper we describe the background, research design, and intervention components of an ongoing project funded by the US National Institute on Drug Abuse (R01DA037628) that is intended to develop and test the usability, feasibility, and efficacy of an Internet-based version of the Family Check-Up (FCU) program as a universal prevention intervention that targets middle school children. In [Multimedia Appendix 1](#) we present the summary statement generated by peer reviewers in the US National Institute on Drug Abuse Study Section prior to our research being funded.

Efficacy of the Family Check-Up Program

The FCU is a strengths-based, family-centered intervention that promotes family management and parent skill enhancement and addresses child and adolescent adjustment problems [10]. It has two components: (1) an ecological strengths-based self-report assessment of child behavior, parenting skills, family dynamics, and life stressors, followed by focused feedback; and (2) parent management training, which focuses on supporting positive behavior, setting healthy limits, supervision, and building

relationships [11]. Depending on the particular program configuration used, the FCU family feedback session can be held at the family home, a clinic, a school, or a community center, and its delivery is typically facilitated by a counselor or coach (in school settings) or a therapist (in community mental health settings). The FCU can be delivered as both a preventive checkup and as an intensive intervention for high-risk families.

Multiple federally funded grants have examined the FCU in randomized controlled trials based in public schools that involved ethnically and socioeconomically diverse young children and middle-school-aged youths [10,12-15]. Strong effects have been found on both proximal and distal outcomes, including substance use, health behavior, and depression. The FCU delivered in middle school has been linked to long-term improvement in academic outcomes (self-regulation, grade point average, school attendance and engagement, and teacher-rated child problem behavior over time) [14,16,17] and various nonacademic outcomes (eg, depression, substance use, and high-risk sexual behavior) [17-20]. It was also related to decreased arrest rates, problem behavior, and substance use. These positive effects have been found to persist through high school and the early-adult years [5,21,22].

The FCU was found to have direct effects on putative mediators, such as youth self-regulation, and on outcomes such as deviant peer affiliation, substance use, and family conflict [17,23]. When the FCU was delivered in schools, teachers reported reduced problem behavior across the 3 years of middle school [14] and in school-related outcomes [24]. The putative mediators associated with changes in behavior across these intervention trials included parenting skill enhancement and youth self-regulation [17,23], with a particular focus on positive parenting across the life span. Improved self-regulation during the middle school years predicted reduced risk behavior during the transition to adulthood more than 10 years later [20].

Electronic Health Interventions

Electronic health (eHealth) interventions delivered via the internet are rapidly being developed for a wide variety of target behaviors, and they have shown encouraging efficacy in controlled trials, for example, for smoking cessation [25-27], depression treatment [28-30], and obesity management [31,32]. These programs can be stand-alone (fully automated), which reduces their cost of delivery while greatly increasing their reach (their public health impact), or they can include live contact with coaches or counselors in face-to-face sessions or through telephone calls [33], which increases participant adherence through accountability to a coach who is seen as trustworthy, benevolent, and having expertise. Mohr et al [33] posited a model of *supportive accountability* that describes how participant engagement and follow-through in eHealth interventions can be encouraged by the human support provided by a coach, for example, when participants receive brief calls from the coach. Using the term *coach* implies that the coach's interaction with families need not require the skills of a highly trained clinician [34]. This level of coach support has been found to enhance the efficacy of eHealth interventions for tobacco cessation [35-37] and depression [38-40].

A number of studies have examined Web-based parent-training programs. Some programs have adopted a video teleconference approach to enable coaches or therapists to observe family interactions and guide treatment activities at parents' homes (eg, the work of Comer and colleagues [41-43] on internet-facilitated Parent Child Interaction Therapy). Other parent-training programs include multimedia and program content designed for parents to use on their own or under the guidance of trained coaches. Examples of these studies are Incredible Years [44], a mobile phone-based version of Helping the Noncompliant Child [45], a Web-based implementation of the Strongest Years program delivered in Sweden [46], the Parenting Wisely program [47], some of the tests of the Triple-P Online program [48,49], and ezParent, a tablet-based intervention designed for a low-income, ethnic minority population of parents [50].

Rationale for the Project

Although a variety of parent interventions in public schools have motivated positive change in parenting and reduced problem behavior [12,51,52], few children and adolescents ever receive treatment for these problems when interventions are fully disseminated, and only a very small percentage of parents participate in parenting or family interventions to address behavioral problems [53,54]. Several likely reasons could explain this problem, including inadequate funding for implementation, schools' competing priorities, complicated logistical requirements for treatments, inadequate time for teachers and staff to be trained and to deliver the program, and parents who are difficult to recruit [55,56]. In a randomized effectiveness trial of the FCU model, we found that schools

were unable to administer the FCU to families in a systematic way, although schools were generally supportive of delivering family-centered interventions from the school. The lack of trained staff and time for implementation were key factors that limited the uptake of the intervention, which was associated with improved outcomes for high-risk students, such as increased parental monitoring and decreased negative school contacts, despite poor implementation [20,57]. This research inspired our efforts to develop an eHealth intervention version of the FCU that could be administered to families with little or no staffing from schools. We used an iterative approach to development that was guided by family and school focus groups, testing of the eHealth version, and adaptations based on feedback. In the next section, we describe our development process, intervention modules, and study design.

Methods

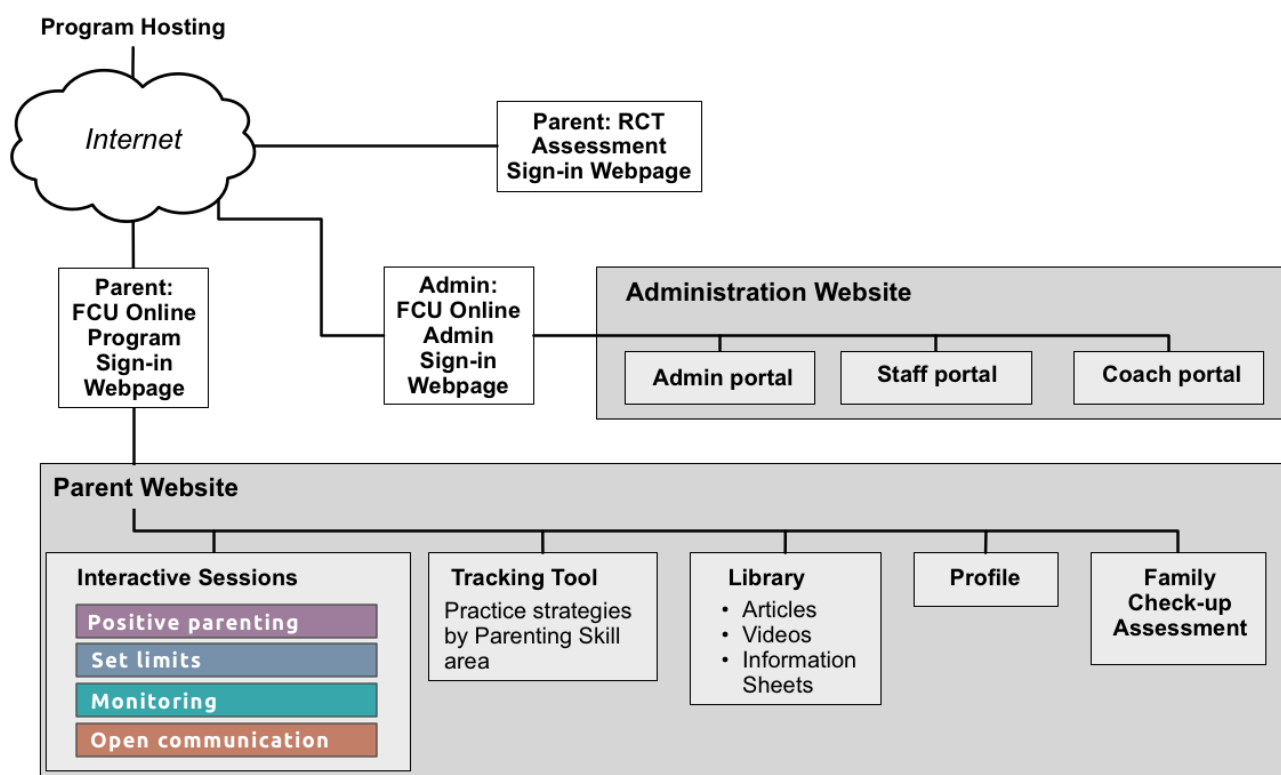
Technology Development Process

We used an integrated technology architecture for the FCU Online website, its administration website, and coach portal, which involved sharing a common database. This resulted in a seamless development process that enhanced quality control and user data tracking. Program components were fully tested on a preproduction server before being moved to the live production environment.

Program Components

The FCU program comprises 3 separate but complementary entities: assessment and feedback, skills sessions in the parent website, and an administration website (Figure 1).

Figure 1. Conceptual schematic highlighting 3 Family Check-Up (FCU) Online components: the parent website, the administration website for managing administration (Admin) and staff, coaches, and guests, and the randomized controlled trial (RCT) assessment website that parents access to complete assessments.



Family Check-Up Program Online Assessment and Feedback

The namesake activity for the FCU is the 88-item, 23-webpage FCU assessment that participants complete as their initial step in the program. This assessment incorporates items and subscales from the Strengths and Difficulties Questionnaire [58] augmented with additional items drawn from other sources and content developed internally by the Oregon group [59]. Once participants submit their completed assessment, they receive feedback in a printout arranged according to major themes and 3 colors that convey how their child and family data compare with normative data (ie, normal, borderline, and clinical ranges). Feedback is guided by motivational interviewing principles, and it provides choices for treatment options and highlights strengths and potential areas of improvement [10]. *Green* highlights a family's areas of strength that, when continued, will have a strong positive impact. *Yellow* signals that an area could use some attention. It does not always mean a significant problem but, if ignored, the problem behavior could escalate. *Red* indicates that an area may be a serious concern for their child or family. If no attempt is made to work on and improve serious concerns, the behavior is unlikely to improve on its own. Feedback also conveys practical changes parents can make to improve their child's behavior and the quality of their family's interactions.

Skills Sessions Website

Once they complete the online checkup assessment and receive related feedback, participants in the FCU Online program are able to access a set of 4 Web-based skills sessions designed to improve the ways in which they interact with their children through skills-based learning. The sessions provide the basis for personalized behavioral adjustments that can directly lead to improvement in overall family well-being. The skills sessions are the following:

- Positive parenting (Figure 2): reinforcing positive behavior through use of encouragement and praise; learning to give directions in a clear and simple way with follow-through; using rewards and incentives to reinforce desirable behavior.
- Setting limits (Figures 3 and 4): creating reasonable rules that clearly state desired behaviors and following up with predefined consequences when children do not cooperate, including consistent reinforcement of compliance.
- Monitoring: recognizing potential risks associated with increased unsupervised time that children may experience during adolescence, and improving monitoring practices to support success at home and at school.
- Open communication: using open communication and understanding that it is key to having positive family relationships; using effective parenting skills, such as listening to their children, asking questions, and problem solving.

These 4 parenting skills sessions use online engagement activities (see Table 1) that are designed to encourage the user

to interact with, and be engaged with, the program. We have developed and confirmed the value of similar engagement activities in our earlier research on eHealth interventions [28-30]. Engagement activities include host videos, dyad videos that model right ways and wrong ways, animations (bear videos) that model right ways, and animated explanation of self-management and problem solving. The program also uses automated text messaging (short message service [SMS]) and emails to push or proactively send program content to users rather than relying only on the parents' initiative to access the intervention [60,61].

Engagement activities include host videos, dyad videos that model right ways and wrong ways, animations (bear videos) that model right ways, and animated explanations of self-management and problem solving (Figure 5). The program also pushes prompting messages using automated text (SMS) messaging and emails [60]. Figure 6 shows the online tracking tool.

Other features include a Library (on the Tab menu) that provides articles about relevant topics (eg, cyberbullying, sibling rivalry, and healthy courtship), videos drawn from the skills sessions, and information sheets that can be printed and saved to computer devices for later reference; a Profile (on the Tab menu) that enables participants to update their personal program information, which contains personal information used by the program (eg, names, addresses, passwords, and mobile phone number); and a checkup summary (button on the home page) that helps participants see how they score overall on their checkup assessment and on specific checkup items (Figure 7).

Family Check-Up Online Administration Website

The FCU Online program administration website varies its display of program content on the basis of user credentials. Specifically, study administrators and staff are able to see a list of participants by their name, their unique study identifier, their phone number, their email address, the target child's name and school, and other descriptive fields. Coaches are able to view only their assigned cases in the coach portal (Figures 8 and 9). Designated guest users are able to review only the features of the website by examining a test case that was created solely for this purpose.

Randomized Controlled Trial

Study Design

In this ongoing study, families meeting eligibility criteria are individually randomly assigned (allocation ratio of 1:1:1) into 3 study conditions: FCU Online-only (n≈100), FCU Online + Coach (n≈100), and a waitlist control condition (middle school as usual; n≈100). Assessments are conducted at baseline, 3 months following randomization (posttest), and at follow-ups scheduled for 6 months following randomization and 12 months following randomization. Figure 10 shows the projected Consolidated Standards of Reporting Trials diagram of study participants.

Figure 2. The Family Check-Up Online skills session for participants on positive parenting. Image shows top menu, left navigation, list activity for choosing skills, text messaging opt-in, video model, and additional information features (helpful tip and research says).

Family Check-Up Online

HOME SKILL SESSIONS TRACKING TOOL LIBRARY CONTINUE CHECK-UP PROFILE LOG OUT

Positive parenting

- Encourage & praise
 - Introduction
 - Choose skills**
- Give directions
- Use rewards
- Summary
- Practice skills

Set limits

Monitoring

Open communication

Choose ways to use encouragement and praise

Think about how often you praise your child. If you're like many other parents, you might not be finding much to encourage and praise these days. Sometimes it can be really difficult to notice the positive things your child does. But letting your child know you see their positive behaviors actually improves their behavior and strengthens your relationship.

Choose strategies to increase

Use the list below to write down how you are going to encourage and praise your child. You can also click the blue List button to choose from ideas that other parents have used in the past. You will get the chance to practice and track these skills a little bit later on in the program.

Ways to encourage & praise ?

- Pat Sam on the head or shoulder [list](#)
- Say: What a terrific idea! [list](#)
- Tell Sam: Thanks for being so responsible and getting home on time! [list](#)
- Say: Great job checking in after school! I really appreciate it. [list](#)
- Giving Sam morning clothes that I warmed in dryer [list](#)

Text messages

When you're trying something new it can be helpful to be reminded to practice. If you would like to receive text message prompts to help you practice praising your child, check the box.

Yes, send me text reminders

When this box is checked, you will receive messages for about 2 weeks. If you want to start receiving them again, then return here or go to the Tracking Tool to re-check the box. You can always opt out by unchecking the box.

Remember to look on the right side of this page to watch videos and see more information by clicking the buttons. Then you're ready to click the Next button to learn more about how to give effective directions when talking to your child.

[← Back](#) [→ Next](#)


Common encouragement and praise situations


Helpful tip

Research says

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Figure 3. The Family Check-Up Online role-playing activity located in the participants' set limits skills session. Image shows a role-playing activity after the participant has typed in content adjacent to the "You say" box, which triggers display of a recommended response.





HOME
SKILL SESSIONS
TRACKING TOOL
LIBRARY
CONTINUE CHECK-UP
PROFILE
LOG OUT

Positive parenting

Set limits

- Clear rules
- Consequences
- ↓ **Challenges**
 - Introduction
 - **Role-play**
- Summary
- Practice skills

Monitoring

Open communication

Role-play how to handle situations

Now take the skills and tips you learned and imagine some challenging situations you might experience with your child. Think through how you might respond by restating your limits and listing the consequence.

Start by reading the following example.

Sample situation: review

Parent says...	Please put your clean clothes away before dinner.
Child says...	Putting clothes away is stupid! I'm busy right now anyway.
Parent says...	I know you're busy, but I asked you to put your clothes away and I need you to follow the rules. You'll lose screentime tonight if you don't get it done before dinner.

Now it's your turn. Click the Start button on each of the two role-playing activities below.


Role-play #1

Parent says...	Please clean your room before you go to Jake's tonight.
Child says...	I don't have time! My show is on in 10 minutes and then I have to leave.
You say...	[[Participant types in content here]]

Recommended response: The direction is to clean your room before you go anywhere else, so please check back with me when your room is clean. Thank you!

How does your response compare?

Restart



Helpful tip

Figure 4. The Family Check-Up Online sorting activity located in the participants’ positive parenting skills session. Audio and written messages ask participants to drag the highlighted sample direction to a box indicating whether it is helpful or unhelpful. The program provides detailed audio feedback until all sample directions have been addressed.

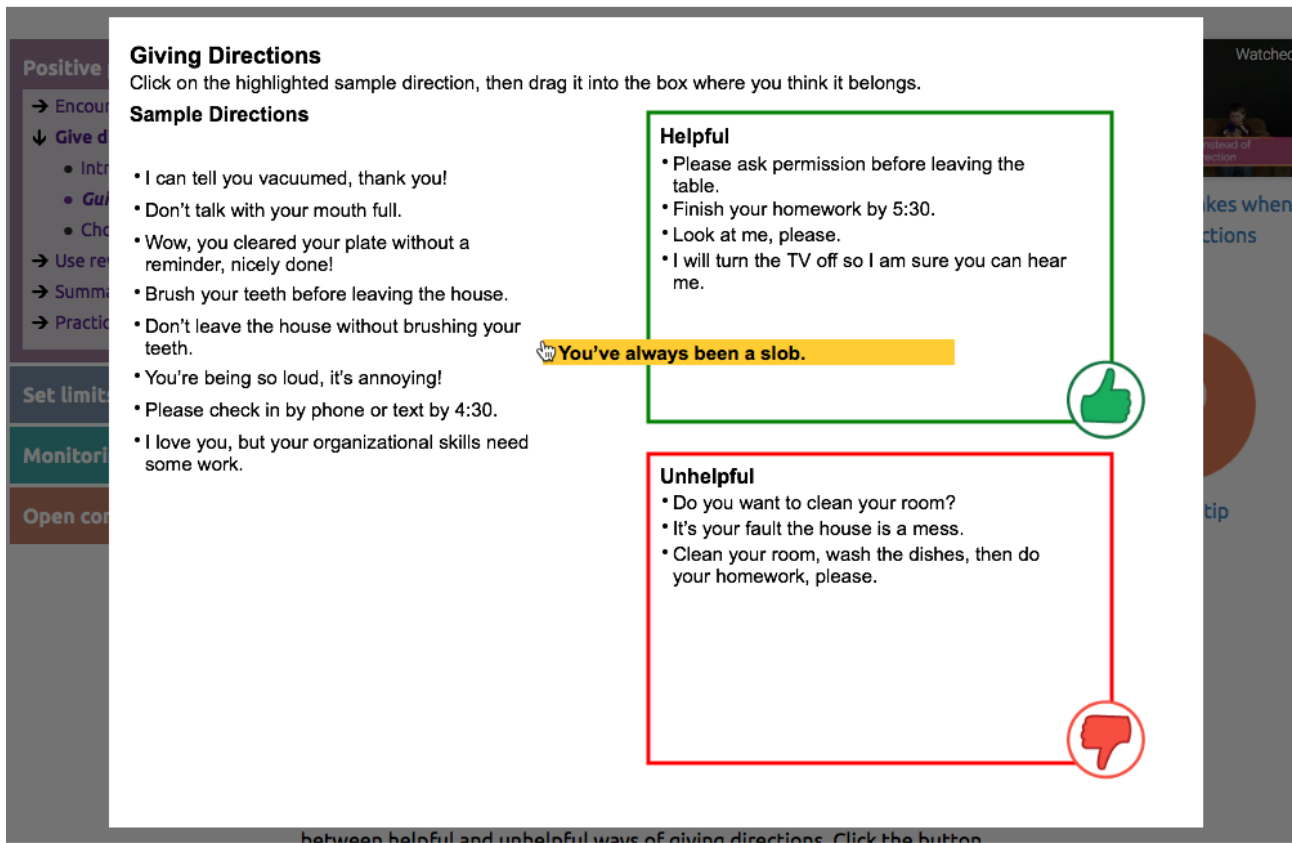


Table 1. Participant engagement activities in the Family Check-Up Online program.

Activity	Function	Examples
List activities	Encourage creation of personal lists to gain insight into their situation	Lists of ways to encourage praise, give directions, and give rewards; household rules; consequences; monitoring skills; school support monitoring skills; active listening skills
Role-playing activities	Practice step-by-step situations and responses	Handling challenging situations; communicating by listening to facts and connecting with feelings
Drag-and-drop activity	Provide an interactive experience to more clearly distinguish between topics	Activity focusing on the difference between helpful and unhelpful ways of giving directions
Online behavior tracking	Web-based tools used to capture participant data over time designed to encourage self-monitoring, to illuminate patterns, and to show progress	Daily tracking of mood ratings and pleasant activities accomplished; these tracked data are also charted online
Wizard/calculator	Tool to help plan schedule	School on-time calculator
Animated tutorials	Animations used to provide an explanation for underlying models for change	Tutorial showing self-management model of trying out new activities, tracking to see if they help, refining them accordingly
Tracking tool	Tool for managing personal practice of recommended strategies and skills	Tool to help monitor activities that are being worked on in each of the major skills areas, ratings for how that practice is going, and ability to edit and update as needed

Figure 5. Example of both the animated bear video and the more traditional video model located on the participants' Family Check-Up Online open communication skills session.

Family Check-Up Online

HOME SKILL SESSIONS TRACKING TOOL LIBRARY CONTINUE CHECK-UP PROFILE LOG OUT

Positive parenting

Set limits

Monitoring

Open communication

- Active listening
- ↓ **Family meetings**
 - Introduction
 - **Meeting guidelines**
 - Choose meeting skills
- Summary
- Practice skills

Family meeting guidelines

To set up a family meeting, find a neutral time and location. Also be sure to set aside enough time for the meeting, at least 15 minutes. Then follow these steps:

1. Describe the family problem neutrally, using a calm voice.
 - Don't try to solve hot issues right away.
2. Take turns coming up with potential solutions.
 - Don't judge any ideas while you are brainstorming.
3. Work with your child to list the pros and cons of each potential solution.
 - Make sure to listen to your child's opinions.
4. Agree on a solution to try out.
 - Remind your child that the solution can be changed if it doesn't work.
5. Choose a date and time to check-in about how the solution is working.

We have found that Family Meetings are one of the hardest skills for families to learn. Watch how the Bear Family uses the guidelines above to work together to solve a big problem.

Using neutral problem statements (0:50)

Helpful tip

← Back **→ Next**

Figure 6. The Family Check-Up Online tracking tool that excerpts strategies (list items) that participants choose to change in each of the 4 skills sessions. It displays an opt-in checkbox for receiving text messages (chosen by type of skill), stars for rating value or helpfulness of each type of skill, and daily practice indicators. Participants can edit and update the contents of this form at any time.

Tracking tool

Help

Positive parenting

 Yes, send me text reminders LESS ↑

	Strategy	Click for each day used						
		#1	#2	#3	#4	#5	#6	#7
Encourage & praise ★★★★☆	Pat Sam on the head or shoulder	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Say: What a terrific idea!	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Tell Sam: Thanks for being so responsible and getting home on time!	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Say: Great job checking in after school! I really appreciate it.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Giving Sam morning clothes that I warmed in dryer	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Give directions ★★★★☆	Complete your homework by dinnertime each evening	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Take out the garbage on Wednesday after dinner.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Complete evening homework by dinnertime and the nighttime	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Don't use smartphone until after homework is finished	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Use rewards ★★★★★	Home resources: Use electronics, take bottles in for refund, Choose TV program/game, Other	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Time with each other: Play a game, Read together, Watch movie together, Cook together, Other	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Set limits	<input checked="" type="checkbox"/> Yes, send me text reminders	MORE ↓
Monitoring	<input checked="" type="checkbox"/> Yes, send me text reminders	MORE ↓
Open communication	<input checked="" type="checkbox"/> Yes, send me text reminders	MORE ↓

Figure 7. The Family Check-Up (FCU) Online check-up summary report available to participants by clicking on a button located on the FCU home page. A similar report is available to coaches in their administration website. This image shows child behavior scores displayed by color of calculated importance. It also shows drill-down detail (accessed by clicking on the blue text link labeled “See more detail”) listing check-up items and related responses that contributed to the scores.

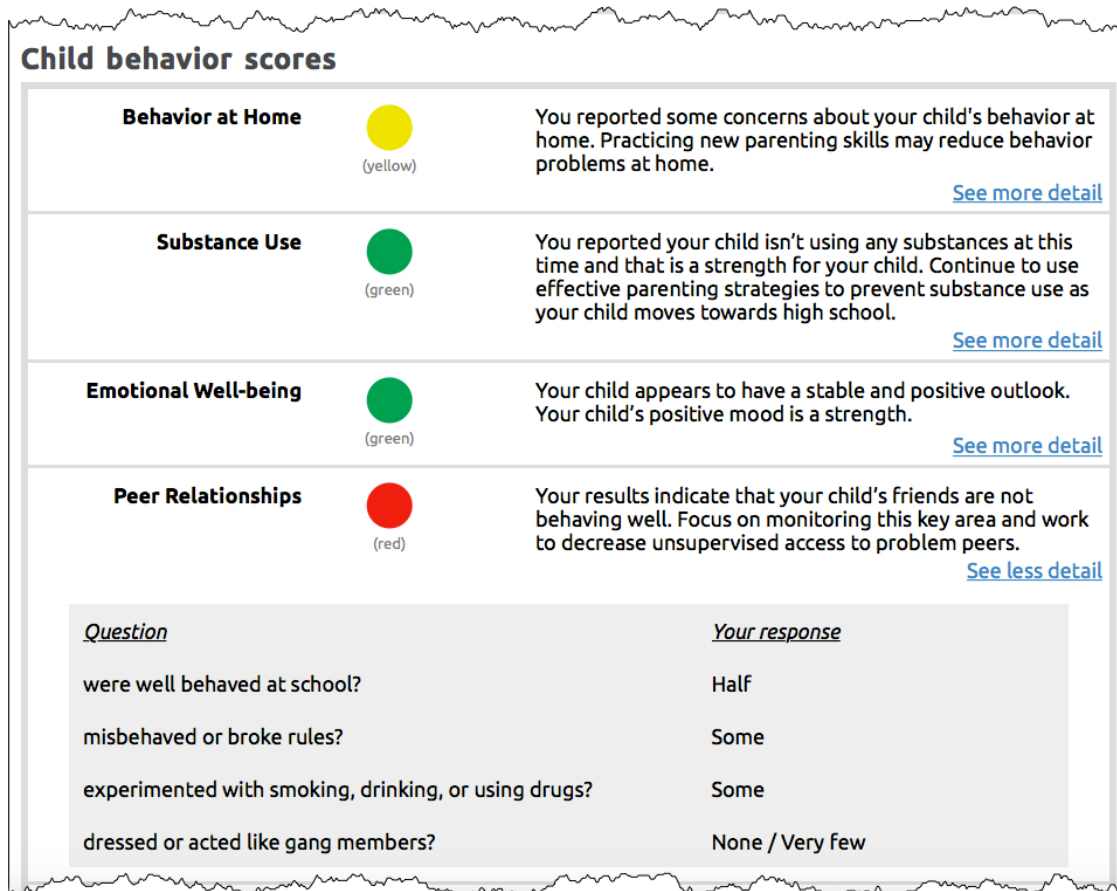


Figure 8. The Family Check-Up Online administration website form used by coaches to describe participant details. It includes fields at bottom of page for jotting down freeform notes and keeping track of key dates and times for coach calls and the check-up results call. ID: identifier; PC: parent caretaker; TC: target child.

Participant Details
Engagement Data
Check-up Summary
Manual Emails

<p>Study ID</p> <input type="text"/>	<p>Current grade</p> <input type="text" value="6th grade"/>
<p>PC First Name</p> <input type="text"/>	<p>School name</p> <input type="text" value="Middle School"/>
<p>PC Last Name</p> <input type="text"/>	<p>Home phone</p> <input type="text"/>
<p>Registration Date</p> <input type="text" value="11/21/2017"/>	<p>Cell phone</p> <input type="text" value="(541) 690-7024"/>
<p>PC Relationship to Child</p> <input type="text" value="Great aunt"/>	<p>Time preferred to be called</p> <input type="text" value="10AM-12PM"/>
<p>TC First Name</p> <input type="text"/>	<p>PC email address</p> <input type="text"/>
<p>TC Last Name</p> <input type="text"/>	<p>Treatment Group</p> <input type="text" value="Web + Coach"/>
<p>TC Gender</p> <input type="text" value="male"/>	<p>Coach name</p> <input type="text"/>
<p>Preferred pronouns</p> <input type="text" value="he / him / his"/>	<p>Special Word</p> <input type="text"/>

Notes

Date of Next Coach Call	Time of Next Coach Call	Date Coach Completes Results Call
<input type="text" value="1/18/2018"/>	<input type="text" value="12:30 PM"/>	<input type="text" value="12/12/2017"/>

Cancel
Save

Figure 9. The Family Check-Up Online administration website form for coaches and administrative staff to review measures of participant engagement in using the program, showing data that are collected unobtrusively.

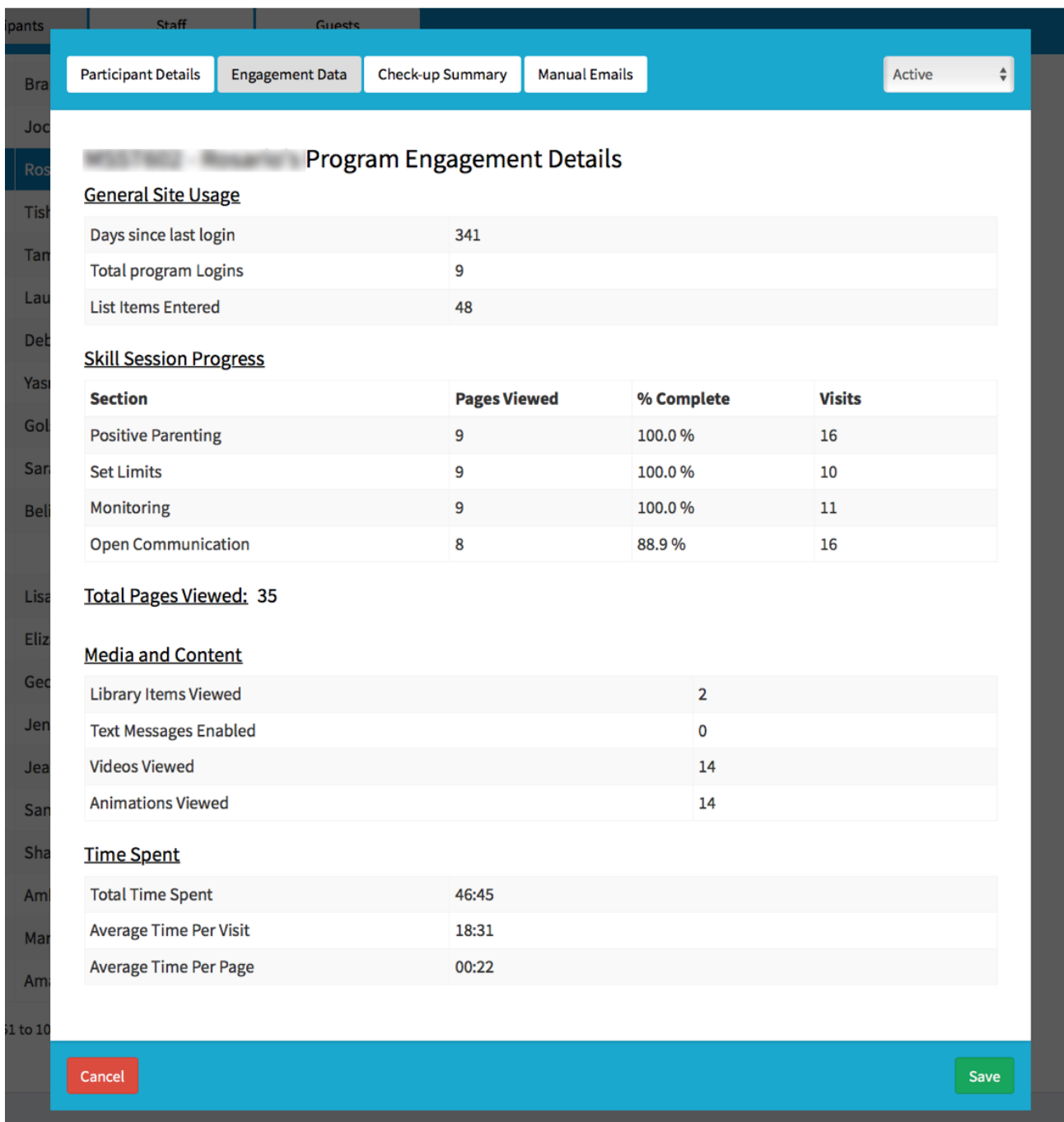
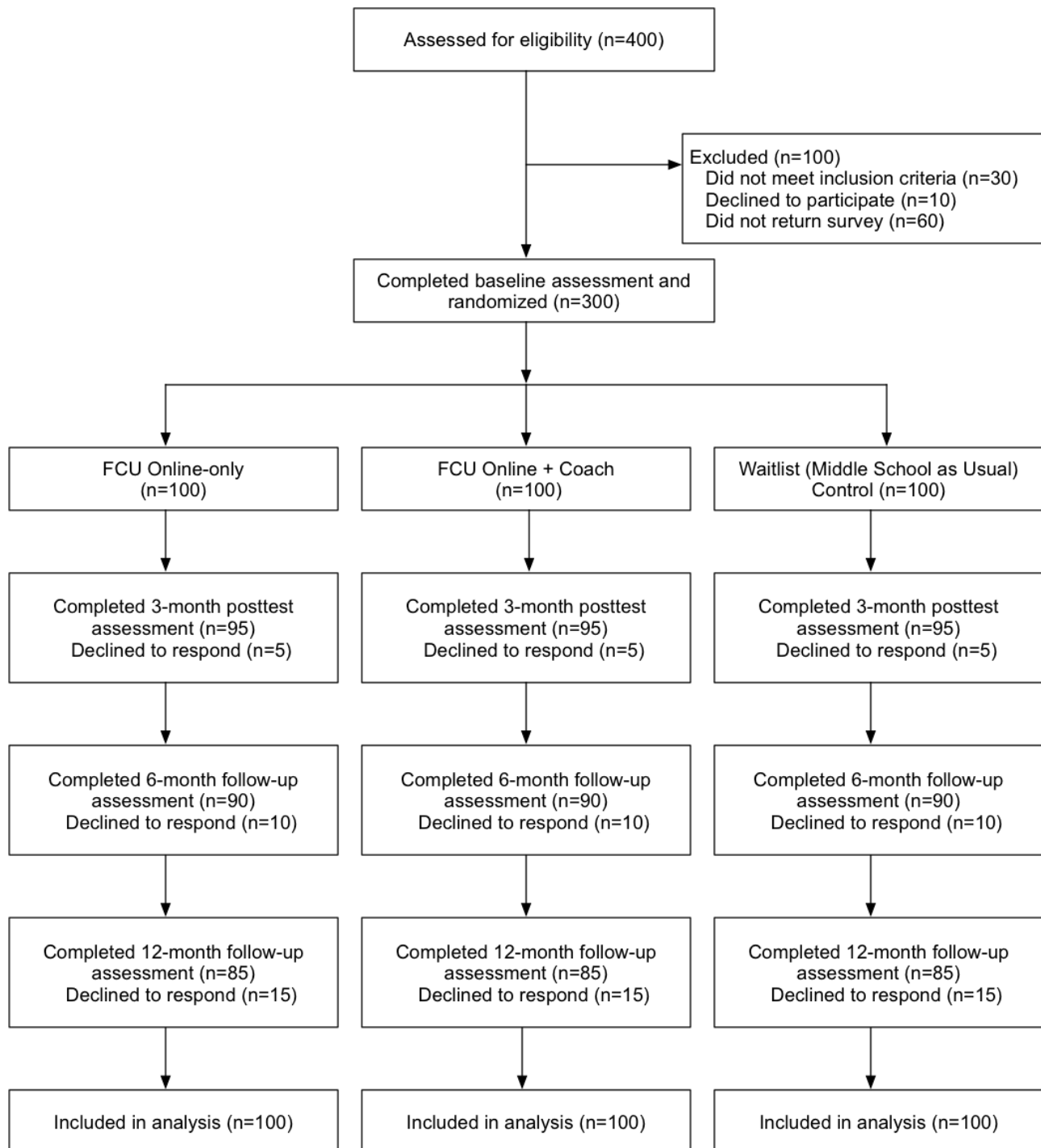


Figure 10. Consolidated Standards of Reporting Trials (CONSORT) diagram of study participants (projected). FCU: Family Check-Up.

Participant Recruitment and Screening

Recruitment has been completed. The research sample is intended to be approximately 300 families recruited from 8 economically disadvantaged middle schools in Oregon, USA, defined as schools that exceed the state average of 55% of students qualifying for free and reduced-price lunch. We drew 2 schools from urban settings, 4 from suburban settings, and 2 from rural areas in the state. Families in these 3 settings may have different community norms regarding parenting behavior and different degrees of access to mental health services or support for positive parenting. They may also use Web-based

resources with different frequency. We are seeking to understand whether community characteristics have an impact on the uptake of an eHealth parenting intervention.

We recruited participants during 2 school years (2016-2017 or 2017-2018) and are currently finalizing our sample. Approximately 150 families of sixth- and seventh-grade students were recruited each year. All families in the designated schools and grades were eligible to participate. Inclusion criteria specified that parents or primary caregivers be legal guardians of the enrolled student and have Web access at home or be willing to access the Web via computers located in the school,

public library, or work, and that they have proficiency in English. Families of students with severe developmental disabilities or physical disabilities (eg, autism, genetic disorders, or Down syndrome) were excluded from the study. We expect the ethnicity of the sample to be consistent with that of families in Oregon: about 78% white, 12% Latino, 5% Asian American, and 5% African American.

Institutional review board–approved study procedures took into consideration the privacy protections outlined in the US Family Educational Rights and Privacy Act [62]; University of Oregon Institutional Review Board Protocol Number: 07032014.004).

The recruitment process began with an email sent to parents of sixth- and seventh-grade students from the principal at each school that included a brief description of the study, stated the enthusiastic support of school staff for the project, and included a link to a secure website where interested parents were asked to provide their contact information. A paid research staff member then called all respondents to screen for eligibility, determine parent preference for receiving materials in English or in Spanish, explain the goals of the study, and provide details about participation.

Families who indicated an interest in the study and satisfied eligibility criteria were mailed a packet that included a parent consent form, a youth assent form, the parent and youth surveys, and 4 self-addressed, stamped envelopes so that each consent and survey could be mailed back separately to project staff. This preassessment included standard, widely used questionnaires that ask about the child's abilities and behavior, parenting practices, family dynamics, family demographics, family health behaviors, and life stressors and took about 30 minutes to complete. One week after this packet was mailed, a research staff member called the parent or caregiver to answer any questions about the consent form or the survey. If the family had not yet returned their surveys, they were reminded to do so as soon as possible.

Randomization to Conditions

Once we receive the completed surveys and consent forms, we randomly assign participating families to a condition within the school such that each school will have a similar number of participants in each of the 3 conditions: FCU Online-only, FCU Online + Coach, and a waitlist control. Spanish-speaking parents who previously indicated comfort reading in English are randomly assigned to 1 of these conditions; parents who indicated greater comfort reading in Spanish are assigned to a nonexperimental telehealth treatment condition that receives print materials in Spanish and interacts with a coach in Spanish.

In the FCU Online-only condition, participants receive a welcome email with an explanation about the website and instructions for logging in. Once they log in to the FCU Online website with their credentials, participants are able to complete the FCU assessment, receive feedback, and then access the skills session website, where they are provided with online tools to support their parenting in areas identified as challenges. These tools include videos, animated videos, parenting tips, and interactive activities (see Program Components section of this paper). Parents are also given the opportunity to practice

parenting skills and track their progress. Parents can receive text messages that prompt them to try out new skills learned from the website. Parents can log in as often as they like and interact with any of the parenting skills sessions on the website.

In the FCU Online + Coach condition, participants receive a welcome email with an explanation about the website, instructions for logging in, and the name and email address of the coach who will be working with them. Participants in this condition log on to the same FCU Online program and follow the same procedure made available to participants in the online-only condition. However, they are also assigned a family coach who calls them at least two times to help establish goals, talks them through their results, offers support, and helps motivate parents to improve parenting practices. These coaching calls are intended to be brief and focused, and to last as long as necessary, but typically for less than 30 minutes. Coach calls are scheduled based on a family's availability, and they may be initiated by either the coach or parent.

In the waitlist control (middle school as usual) condition, participants receive an email thanking them for their participation and letting them know that project staff will next contact them in 3 months, when they complete another questionnaire.

Measures

Families in all 3 conditions are mailed a follow-up questionnaire at 3 months, 6 months, and 12 months that is identical to the preassessment in order to assess changes in constructs over time (see Table 2). Each follow-up questionnaire is estimated to require 30 minutes to complete. The 3-month follow-up questionnaire for parents in the 2 intervention conditions also includes a 2-page website feedback survey that requires approximately 10 minutes to complete. All families receive remuneration for their time: US \$100 for completing the baseline assessment and US \$100 for completing each of the 3 follow-up assessments, for a total of \$400. Families can also earn a US \$50 bonus if they complete all 4 assessments.

Sociocultural Contexts and Resources

Family resources and contextual stressors are assessed. Background variables are obtained from primary caregivers by using our project-generated Demographic Questionnaire, which includes queries about family income, parents' occupational status, education, marital status, living situation, and parenting arrangements, if any. Parent and child physical health are also assessed, as is social service use. In addition, parental emotional well-being (depression and anxiety), substance use, and relationship satisfaction are assessed.

Parent physical health is assessed with 3 items regarding height, weight, and perception of general health. Child physical health is assessed with 5 items taken from the Child and Family Center Student Survey (CFCSS) [63] regarding height, weight, perception of body size, consumption of soda and sweet drinks, and daily exercise. In addition, the family's engagement in healthy food choices and physical activity is assessed with a 31-item modified version of the Family Health Behavior Scale [64].

Table 2. Assessment timeline.

Constructs	Baseline	Posttest (3-month assessment)	Follow-up (6- and 12-month assessments)
Family sociocultural contexts and resources			
Family income	P ^a	P	P
Parent's occupational status	P	P	P
Parent education	P	P	P
Parent marital status	P	P	P
Living arrangements	P	P	P
Parenting arrangements	P	P	P
Parent physical health	P	P	P
Child physical health	P	P	P
Family health behaviors	P	P	P
Parent anxiety and depression	P	P	P
Parent substance use	P	P	P
Parent relationship satisfaction	P	P	P
Service use	P	P	P
Parenting skills and behavior			
Setting limits	P	P	P
Monitoring of peer relationships	P, C ^b	P, C	P, C
Monitoring of family routines	P	P	P
Positive parenting	P, C	P, C	P, C
Parental involvement in child's school	P	P	P
Parent self-efficacy	P	P	P
Youth adaptation and family outcomes			
Youth problem behavior			
Child's effortful control	P, C	P, C	P, C
Youth adjustment to school	P, C	P, C	P, C
Strengths and Difficulties Questionnaire	P, C	P, C	P, C
Child substance use	P, C	P, C	P, C
Child attitude about substance use	C	C	C
Child association with deviant peers	P, C	P, C	P, C
Family relationships			
Family conflict	P, C	P, C	P, C
Positive family relationships	P, C	P, C	P, C
Positive family support	P, C	P, C	P, C
Family engagement			
Program use ^c	P	P	P
Website satisfaction	—	P	—
Coach calls ^d	P	P	—

^aP: parent.^bC: child.^cProgram use was monitored automatically and unobtrusively by the intervention website over the course of the project period.^dA coach phoned participants in the FCU Online + Coach condition at least two times in the period between baseline and posttest.

Parental emotional well-being is assessed using the 2-item Patient Health Questionnaire depression screener [65] and the 2-item Generalized Anxiety Disorder Scale screener [66]. Parents' use of tobacco, alcohol, and marijuana is evaluated with a brief 3-item version of the Parent Substance Use Questionnaire [12]. Parental relationship satisfaction is assessed using the 4-item screening version of the Dyadic Adjustment Scale short form [67,68]. Finally, service use is assessed using 7 items adapted from the Services Assessment for Children and Adolescents [69] regarding mental health, medical, or school services received in the past year by the child, primary caregiver, or other household member.

Parenting Skills and Parenting Behavior

Parental skills and behavior are assessed using both parent- and child-report measures. Parents report about setting limits with 7 items excerpted from the Parenting Children and Adolescents measure, an unpublished older-child version of the Parenting Young Children measure [70]. Monitoring of peer relationships, monitoring of family routines, and positive parenting is measured with 21 items adapted from the Parent Interview [71,72]. Youth also report about positive parenting and parental monitoring of peer relationships with 13 parallel items adapted from the CFCSS [63]. Parental involvement in the child's school and parent self-efficacy are also assessed through parent self-report via 6 items from the Parent Involvement Scale [73] and 8 items adapted from the Parenting Task Checklist [74].

Youth Problem Behavior and Adaptation

Parents and youth report about the teen's effortful attention control via an 8-item subscale of the Early Adolescent Temperament Questionnaire [75,76]. Parents and youth also report about the youth's adjustment to school by using 5 items adapted from a measure of school participation [57]. Problem behavior is assessed through several modalities. Parents and youth report about problem behavior using the 26-item Strengths and Difficulties Questionnaire [58]. Child substance use is assessed with 3 parent-report items about the frequency of their child's tobacco, alcohol, and marijuana use and with 4 child-report items about tobacco, alcohol, and marijuana use in the past month and about riding in a car with someone under the influence. Children also report about the perceived difficulty of obtaining tobacco, alcohol, or marijuana (3 items) and their attitudes regarding these substances (3 items), adapted from the CFCSS [63]. Child association with deviant peers is also assessed via parent and child report with 4 items adapted from the Peer Affiliation and Social Acceptance measure [77].

Family Relationships

Parents and children both report about family conflict, positive family relationships (4 items), and positive family support (3 items) [78].

Family Engagement

Family engagement with the intervention is assessed in three ways. First, we look at participant use of the eHealth intervention. Each participant in each of the 2 intervention conditions determines how often and for how long they interact with the program, which is assessed unobtrusively by the program. Following an approach we used in earlier research on

eHealth interventions [28,79,80], we created a composite measure of program engagement defined as the product of the z score transformations of the mean of (1) the overall duration of program visits, and (2) the overall sum of the number of visits. These measures also allow us to assess the extent to which each participant used each module in the program by using a more detailed assessment of engagement activities (eg, reviewed videos and animations, opened online documents, created personal lists, or tracked practice activities).

Second, consumer satisfaction with the website is assessed at the time of the 3-month posttest using a measure developed for parent-training programs [81], which includes satisfaction with content and delivery of the model and factors related to uptake and use of the information. We adapted it for this study to also assess barriers parents may face in completing an eHealth intervention (eg, time or computer equipment).

Third, in the FCU Online + Coach condition, family engagement is assessed via the number of contacts with a coach, total minutes of contact with a coach, and overall therapy dosage.

Implementation Assessment

During project year 5, we will assess our effort to encourage the continued implementation of the FCU Online program in schools that participated in the research project. We will train school personnel in both versions (FCU Online-only and FCU Online + Coach) and problem solve with the school to ensure successful uptake, and work with the school to identify families for the intervention by using natural school indicators of success (eg, attendance, behavior referrals, and grades). We will then assess uptake of the intervention by interviewing teachers and administrators about their usage. In addition, we'll use our measure of successful uptake of family-centered, school-based interventions, the Family-School-Wide Evaluation Tool [82], based on the widely used School-Wide Evaluation Tool assessment for evaluating uptake of positive behavior support programs in schools [83,84]. This will occur at the end of year 5 after the schools have had a chance to implement the program throughout the year.

Formative Research Process

At multiple points in the iterative development process, we have gathered information from potential users about what was working in the program and what needed to be adapted or reformulated. The first of these focus groups included 6 parents and the dean of students from a participating middle school. Three other focus groups included various school staff from 4 schools (2 suburban and 2 rural). The first included 2 principals, 2 vice principals, and 1 school counselor; the second included 1 principal, 2 deans of students (1 of whom was also called a family liaison staff), and 1 counselor; and the third included 1 principal, 1 counselor, and 1 behavioral specialist. We integrated the feedback from these groups into the development and design of the program (eg, enable users to go back and retake the FCU assessment, provide more tips and the shorter the better, have children looking at mobile phones in the pictures so the images appear more accurate and up-to-date, allow different credential levels on the administration site).

Next, we conducted usability testing with 5 participants to examine the acceptability and feasibility of the program. Usability testers met individually with a research staff member in 90-minute sessions during which they interacted with portions of the FCU Online program while testers used think-aloud techniques to describe their ideas and thoughts. Usability test participants were also asked to complete the 10-item System Usability Scale [85] to examine the acceptability and feasibility of the program. Items in this scale include “I think that I would like to use this website frequently” and “I thought the website was easy to use.” We then used these qualitative and quantitative data to further improve the design of the program.

Finally, we conducted a pilot study with 7 participants in either the FCU Online-only or the FCU Online + Coach condition. Parents were then given 2 weeks to use the website and meet with a coach (if applicable). Next, parents provided verbal feedback about their experience with the assessment process in general, and with the website specifically, during a debriefing interview with project staff members. This feedback was used to further improve the surveys and program logic.

Data Analysis

Families are randomly assigned to a condition and will be the unit of analysis for all models. Mixed-effects analyses will be based on a hierarchical linear modeling approach in which students are nested within schools; primary outcomes are nested within individual students at level 1 of the model; and between-participant predictors (fixed effects), such as treatment condition and child and parent demographics, will be examined at level 2. This approach will (1) account for the correlated within-participant errors created by nesting of repeated measurements within study participants, (2) allow us to examine longitudinal trajectories within a unified and flexible framework that also facilitates examination of potential moderating and mediating variables, and (3) enable us to test for potential dependencies (school-level effects) in the data. For each of the 3 pairwise contrasts between conditions, we will examine intervention effects by modeling longitudinal trajectories across time with mixed-effects models using SAS PROC MIXED (SAS Institute) or Mplus software (Muthén & Muthén).

Using an intent-to-treat approach with 100 participants per condition, with alpha set to .017 (to adjust for multiple contrasts), there is sufficient power (>.80) to detect a condition effect of Cohen $d=.42$ or larger (moderately small effect size) between either intervention condition and the control group on primary outcomes, which include effective parenting skills and reductions in child problem behavior. Previous FCU efficacy trials have demonstrated medium to large effects for tobacco use, alcohol use, cannabis use, antisocial behavior, and arrest rates [15,21].

Results

This project was funded in 2015 and the research project period is scheduled to be completed in 2020. Participant recruitment was completed in spring 2018 and initial assessment is ongoing. Follow-up assessments will not be completed until 2019.

Discussion

Overview

This paper describes the innovative FCU Online eHealth intervention randomized controlled trial for parents of middle school children. Our report focuses on the background, research design, and intervention components of a trial that will develop and test the usability, feasibility, and efficacy of an eHealth version of the FCU program that targets middle school children. The rigorous study design will allow for comparisons of two versions of the FCU Online program (FCU Online + Coach, FCU Online-only) and the waitlist control condition.

Strengths and Limitations

A fundamental strength of the FCU is that it is scalable at multiple levels, depending on the barriers and resources available (family resources and school resources). For schools, barriers in staffing and coach support may prohibit use of the FCU Online + Coach, and these schools can use the FCU Online-only version, which requires limited staffing support to provide access to families. Barriers for families include time, transportation, and internet access. The FCU Online program can be delivered to families in their home and on their own schedule. The website is accessible by phone and can also be used “on the go.” Schools may also provide computer access to enable families to complete the program. This provides a high-reach, scalable approach to help families that is accessible to urban, suburban, and rural communities.

Another strength of this study is the use of multiple urban, suburban, and rural schools throughout the state of Oregon. This diverse population will allow us to examine rural versus urban participation and consumer satisfaction. We plan to implement the FCU Online program in 1 model school at the end of the study, which will provide additional information about dissemination.

Our development approach is also a strength of this study. Specifically, our use of an integrated technology architecture and a shared database facilitates data sharing and consistent programming procedures for the FCU Online website, its administration website, and its coach portal. Similarly, our use of an iterative formative research development process helped confirm program functionality and refine the program’s user experience design and user interface.

A potential limitation is the financial remuneration of the maximum amount of US \$450 that participants are scheduled to receive in this efficacy trial for time and effort spent completing the assessments. We believe that this level of remuneration is equivalent across conditions and therefore it should not differentially affect groupwise outcomes. Moreover, it is contingent upon assessment completion rather than participation in the intervention. However, given the likelihood that the FCU Online program would not be implemented in the real world with such significant financial consequences, it will be important to assess the FCU Online program within a more practical context. In addition, previous research on the FCU has demonstrated prevention effects emerging over long-term, multiyear follow-up. As such, potential long-term prevention

effects of the FCU may not be detected within the 1-year follow-up period of this study. Another possible limitation is that participants using the current version of FCU Online program must be proficient in English.

Future Directions

Programs such as the FCU Online represent an important next-generation direction in delivering behavioral health programs to parents and caretakers of school-aged children. Previous researchers and clinicians have been working to integrate evidence-based behavioral health prevention and intervention programs (also termed mental health programs) into schools for more than three decades (eg, [86,87]). Nearly all these attempts identified a consistent set of barriers when moving from “hothouse” efficacy demonstrations to the real-life frontiers of community educational settings and service providers. These barriers primarily include lack of resources (particularly in rural settings); stigma and parental resistance associated with behavioral health screening and diagnostic methods [88]; competing responsibilities of intervention staff; lack of support from school administrators and teachers, who often have no exposure to or training in behavioral health practices that are evidence based; difficulty in engaging families; and administrative and staff turnover, which creates a tremendous and ongoing staff training problem. The fact that many evidence-based practices are not flexible in terms of allowing shorter sessions and briefer interventions, and that most are developed for single issues (eg, anxiety, depression, or oppositional defiant disorder), makes it difficult to integrate various behavioral health programs [57,87,89], which creates additional barriers to uptake in real-life community settings.

In the context of all these barriers, schools are faced with increasing challenges, such as climbing rates of mental health issues, high rates of behavioral problems, children exposed to trauma, and school violence [90,91]. The FCU Online program has the potential to help address many of the aforementioned barriers that more traditional school-based behavioral health implementation strategies have yet to solve. For example, strengths of the FCU Online include its ability to be used within any behavioral health service delivery model or strategy (eg, school-only, school plus community behavioral health clinicians, and school-based health clinics), the ability of parents and clinicians to titrate (ie, use indicated modules or the entire

program), and the ability to select families for intervention in a nonstigmatizing manner (ie, nonuse of *Diagnostic and Statistical Manual of Mental Disorders* diagnostic labels). The FCU includes a contextualized assessment of known family, child, and parenting constructs associated with behavioral health and educational outcomes (common elements approach); engagement of parents with multiple and parent-preferred levels as opposed to the more usual face-to-face-only strategies; presentation through multiple methods (eg, human video; video animations; text, graphs, and tools; exercises and forms; and additional literature) of evidence-based parenting methods and exemplars that are not confounded by clinician talent and training; and low response cost for schools to integrate at whatever level their desire or resources allow.

In addition, it remains for additional research to demonstrate the extent to which adding complementary program content (eg, stress management skills training, healthy eating) aimed at parents might enhance impact and whether benefits might accrue from adding online content for children. For example, embedding content from an evidenced-based curriculum, such as Coping Power, that includes both child and parent components into FCU Online might enhance outcomes over time [92]. Additional research on implementation and sustainability of effective interventions might explore whether targeted eHealth interventions for families, such as the FCU Online program, could be but one element of a multicomponent, school-based mental health program that provides access to engaging internet-based resources and tools [93,94]. Future analyses (following the examples set by the recent review by Finan et al [95] and the study by Heinrichs [96]) should also examine the possible impacts of different amounts of behavioral health prevention dollars used (1) to incentivize recruitment and assessment completion and (2) to encourage the practice of program strategies that might sustain treatment effects long after research payments are no longer an option.

Plans for future development of the FCU Online program include more-varied approaches and reporting to accommodate multiple parents and caretakers per child, multiple children within a participating family, expansion of program content for use by Spanish-speaking users, and expansion to health-related topics (eg, obesity management and prevention, and health promotion).

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report: summary statement generated by peer reviewers in NIDA Study Section.

[PDF File (Adobe PDF File), 167KB - [resprot_v7i7e11106_app1.PDF](#)]

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Abbreviations

CFCSS: Child and Family Center Student Survey

eHealth: electronic health

FCU: Family Check-Up

SMS: short message service

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Protocol

Minimally Invasive Dentistry Based on Atraumatic Restorative Treatment to Manage Early Childhood Caries in Rural and Remote Aboriginal Communities: Protocol for a Randomized Controlled Trial

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Abstract

Background: The caries experience of Aboriginal children in Western Australia (WA) and elsewhere in Australia is more than twice that of non-Aboriginal children. Early childhood caries (caries among children <6 years) has a significant impact on the quality of life of children and their caregivers, and its management is demanding and commonly undertaken under general anesthesia. A randomized controlled trial using a minimally invasive dentistry approach based on Atraumatic Restorative Treatment (ART) in metropolitan Perth, WA, has demonstrated a significant reduction in the rate of referral to a dental specialist for dental care among children with early childhood caries, potentially reducing the need for treatment under general anesthesia. The tested approach was clinically successful and was without adverse effects on child dental anxiety. The model of ART-based primary care requires further testing and development if similar outcomes for Aboriginal children in remote and rural settings are to be achieved.

Objective: The study aims to develop, implement, and evaluate a remote primary care model to deliver effective primary dental services, encompassing treatment and preventive services, to Aboriginal preschool children (based on minimally invasive approaches including ART).

Methods: This is a two-arm parallel cluster randomized controlled study in which a test group will be provided with the intervention treatment at the start of the study and a control group will be provided with the intervention treatment 12 months after study commencement (delayed intervention). Participating communities, stratified by size of community (ie, number of

children in the sample frame) and baseline caries experience, will be randomly assigned using a computer-generated block randomized list into immediate (test group) or delayed intervention (control group; provided with standard care). Informed consent will be obtained from all participants. Aboriginal research assistants will explain the study to the parents and assist the parents in completing the questionnaires. Participants in the randomized study will be examined at baseline and at 12 months follow-up by a calibrated examiner. Test group participants will subsequently be contacted and appropriate appointments coordinated for treatment. Control group participants will be provided with standard preventive care by the Aboriginal Health Workers and managed for treatment as per standard procedures.

Results: Community consultations have been undertaken and 26 communities have agreed to participate. Fieldwork is in progress to recruit study participants.

Conclusions: The significance of the study lies in its holistic approach to testing the model of care. Clinical evaluations as well as oral health related quality of life evaluations will be undertaken. Cost-effectiveness and cost-utility evaluations will assist in the development of policy options for oral health services for rural and remote communities. The elicitation of caregiver perspectives through focus group interviews will supplement the clinical, psychosocial, and cost-utility evaluations and provide a richer evaluation of the intervention.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12616001537448; <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=371735> (Archived by WebCite at <http://www.webcitation.org/70UMxndFZ>)

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KEYWORDS

cost-effectiveness analysis; early childhood caries; health utility; health-related quality of life

Introduction

Background

Dental caries in early childhood, or early childhood caries (ECC), has been shown to have a significant impact on the quality of life of children and their caregivers [1]. These effects include symptoms of pain, functional limitations, psychological dysfunction, parental distress, and financial burden. Also, early life dental caries experience is a strong predictor of dental caries in adulthood [2]. Thus, preventive interventions in the early life course are expected to affect oral health in older age. Therefore, interventions at an early age to manage disease in its early stages and effective preventive measures are needed to maintain function and quality of life and to improve oral health in adulthood.

Managing Dental Caries in Early Childhood

Oral rehabilitation for dental caries under general anesthesia (GA) of children with ECC has been shown to improve child oral health related quality of life (COHRQoL) [3]. However, dental treatment under GA does little to prevent the occurrence of new dental decay in these children and they are often readmitted for dental treatment under GA [4]. Thus, treatment and preventive approaches that can be undertaken in primary dental care settings to reduce the number of preschool children undergoing dental GA are urgently required. There is limited information available on COHRQoL outcomes in children after primary dental care for dental caries that suggests modest improvements in COHRQoL [5]. Therefore, there is a need to evaluate changes in COHRQoL after primary dental care.

Comprehensive care under GA is relatively expensive, for the individual and for the community, and is not without risks, including the potential for long-term adverse

neurodevelopmental effects [6-8]. Also, recent reports suggest that oral rehabilitation under GA for children does little to alleviate dental fear or change noncooperative behavior and may in fact heighten child dental fear [9,10].

Potentially Preventable Hospitalizations

Admissions to a hospital for dental care are classified as potentially preventable with timely and adequate non-hospital care [11]. However, there is a trend of increasing hospital admissions for dental care among children, especially among 0-4-year-olds [12,13]. In Australia, this is occurring in spite of the apparent low dental caries experience among children [14,15]. Admissions to hospital for dental conditions made up more than 20% of total admissions for potentially preventable acute admissions in 2013-14 in Australia, second only behind admissions for urinary tract infections [16]. In a recent report, Western Australia (WA) had the highest, and an increasing, rate of hospital admission for dental treatment of all Australian States and Territories among children. Worryingly, the rate among Australian Aboriginal children was twice that of non-Aboriginal children among the 0-4-year-olds [12]. The cost for hospital admission for dental care for children in WA has been estimated at approximately Aus \$9-10 million per year. The mean cost for Indigenous children was significantly higher than the cost of care for non-Indigenous children [6].

Aboriginal Oral Health

A recent report on the oral health of school children examined within the School Dental Service (SDS) in WA showed that Aboriginal children had nearly twice the decay experience of non-Aboriginal children in both deciduous and permanent teeth, and 1.8 times and 2.4 times the number of carious deciduous and permanent teeth, respectively, after controlling for exposure to community water fluoridation and socioeconomic level [17].

Also, although the rate of admission for hospital-based care has increased for Aboriginal children and is now approaching the rate of non-Indigenous children, it is lower for Aboriginal children in rural and remote areas. This has been attributed to lack of access to care due to costs, availability of services, and a lower proportion of Aboriginal children with dental insurance [6].

In WA, nearly two-thirds of the Aboriginal population lives in rural and remote locations, making access to services challenging [18]. The WA Aboriginal Health and Wellbeing Framework identified oral health among the priorities addressing risk factors, along with development of health services tailored to meet the needs of the Aboriginal people underpinned by evidence, based on quality research [18]. The proposed research will evaluate a model of care, which can be translated into mainstream health service delivery, using a strong randomized controlled study design.

A “New” Approach to Dental Caries Management in Early Childhood

The minimally invasive dentistry approach to managing dental caries and its potential role in the provision of public dental services has been described in dental literature [19]. The Atraumatic Restorative Treatment (ART) approach, initially developed to assist dental care delivery in underserved communities, where access to electricity and running water may not be readily available, is now increasingly seen to have relevant applications in subpopulations around the world [20]. Whereas the standard care approach would involve the administration of local anesthesia and removal of dental caries using rotary instruments, the ART approach principally relies on removing affected dentine using hand instruments alone, usually without the administration of a local anesthetic, and restoration of the prepared cavity with a glass-ionomer cement. ART makes provision of dental treatment in very young children, where cooperation for standard dental care approach may be limited, feasible in a primary care setting. It may also reduce dental anxiety among children, thereby facilitating appropriate future dental attendance behaviors [21].

Evidence

In WA, dental therapists, through the SDS and working in school-based dental clinics, have been the mainstay of successful publicly provided dental care for 5-17-year-old school children since the early 1970s [22]. A recently completed pilot randomized controlled trial in WA showed that primary care delivered by dental therapists trained in the ART approach, compared to standard care (ie, dentists providing treatment using the drill and local anesthesia), reduced the rate of referral for specialist pediatric dental care of preschool children affected by ECC by 44% [23]. The ART-based approach adopted in the study relied on treating carious teeth by removing affected dentine using hand instruments without the administration of local anesthetic. However, a pragmatic approach to treatment was undertaken in that the use of rotary instruments was permitted where a clinician judged that the child was able to cope with the procedure after a period of acclimatization to dental treatment. This pragmatic approach enabled the undertaking of more invasive procedures, beyond what standard

ART approach encompassed, such as pulp therapy of deciduous teeth and, in a few instances, tooth extractions.

The study also included a range of preventive interventions including fluoride varnish application to deciduous molars and noncavitated carious lesions as well as oral health counseling using the motivational interviewing approach. The study delivered a “holistic” package of care that considered the needs of the child in total, including preventive care and appropriate skill development of the parent/caregiver to promote oral health. Also, in that study, some children who were scheduled for care under GA were able to be successfully treated using the ART-based approach. The study showed that the COHRQoL was improved after primary dental care with acceptable clinical outcomes [24,25] without adverse effects on childhood dental anxiety. In addition, the approach was cost saving. Hence, the ART-based approach may provide a successful primary model of care, encompassing both treatment and prevention, for children in rural and remote locations where access to GA may not be advisable or readily available.

Current Situation

The WA state government is introducing an early childhood preventive program for preschool children (0-4-year-olds) in rural and remote Aboriginal communities by applying fluoride varnish to the primary teeth by Aboriginal health workers trained in the fluoride varnish application. The fluoride varnish program is incrementally being rolled out throughout WA, starting in Kimberley (north-west WA) in 2016. The program is a preventive program, and children requiring dental treatment are referred to the local dental practitioners, either private practitioners or practitioners within the Health Department or Aboriginal Medical Services. While fluoride varnish application has been shown to be efficacious in ECC prevention among Aboriginal children [26], children without adequate access to treatment services may continue to experience untreated disease.

Currently, preschool children (ineligible for SDS care) requiring dental treatment need to source care from private dental practitioners (ie, at their own cost) or, if eligible for subsidized care (ie, liable for co-payments) through government general dental clinics, where restorative care is provided by dentists. Dental therapist and oral health therapists provide mainly dental hygiene services. Subsidized dental care is available to those who are in receipt of certain types of Commonwealth Government benefits (eligibility for the benefits are means tested). The WA government general dental clinics, located mainly in regional cities and major towns, provide clinical care mainly to eligible adults, but children ineligible for SDS and in receipt of specific types of government benefits are able to access care. The location of these clinics in major regional centers means extensive travel for children living in more remote locations to access care. Also, treatment is usually provided using standard care approaches involving the administration of a local anesthetic and using rotary instruments to prepare the cavity.

Why is this Study Important?

Provision of dental care to preschool children poses significant challenges because of the stage of development and capacity

for cooperation of the young child, and treatment is often provided under GA. The issues are multiplied for Aboriginal preschool children in rural and remote locations where access to specialist dental care is severely limited. Alternative approaches to dental treatment of dental decay in preschool children in primary dental care settings that reduce the need for GA is urgently required. This study will test the hypothesis that Aboriginal preschool children in rural or remote locations can be provided with appropriate dental care using the ART-based approach, without the need for specialist care and can potentially avoid the need for GA.

Our study has six major strengths: (1) it will further develop and evaluate the ART-based model of care, which had been successfully tested in a pilot program in an urban setting in WA, led by author PA, (2) we will develop, for the first time, a dental specific child health utility scale, (3) we will measure the change in clinical parameters as well as the changes in child quality of life and health utility with dental treatment, (4) we will measure the impact of dental treatment on child dental anxiety, (5) we will undertake a cost-effectiveness/cost-utility analysis, and (6) we will ascertain the community acceptability of the tested intervention through focus group interviews. The “holistic” evaluation of the intervention including efficacy and effectiveness of the clinical intervention as well as impact on psychosocial parameters and economic evaluation will greatly facilitate research translation. Also, our research team comprise both world-class researchers who have experience working with the Australian Aboriginal population, and leading policy and service delivery experts, thus ensuring the translation of the study findings into applicable policy, practice, and service delivery in rural and remote locations. We will also be working in collaboration with an Indigenous Advisory Committee and significant community members to provide oral health promotion training to significant community members. This will embed oral health promotion within the communities and ensure sustainability of the oral health improvements after the research has been concluded.

The Kimberley region of WA is geographically large, three times the size of the United Kingdom. Almost the entire region of Kimberley (97%) is classified by the Australian Bureau of Statistics as Very Remote with the remaining 3% as Remote. It also has a higher proportion of Aboriginal people than the rest of the state (45% vs 3.6%). There are hundreds of Aboriginal communities dotted throughout the region, and most are very small with few people. The estimated resident population of the region in 2016 was 36,392 (children 0-4 years was 3274). The region also has high levels of socioeconomic disadvantage with the majority of residents (57%) living in areas with the lowest 10% of the Index of Relative Socio-Economic Advantage and Disadvantage score in Australia [27].

Aims

The principal aim of the proposed study is to develop, implement, and evaluate a remote primary care model to deliver effective primary dental services, encompassing treatment and preventive services, to Aboriginal preschool children (based on minimally invasive approaches including ART). This will be compared with standard care for cost and benefits in terms of

improved dental health and reduced childhood dental anxiety. Our specific aims and hypotheses are:

Aim 1. Measure the proportion of children able to be provided with care without the need for dental specialist referral and the increment in dental caries. Hypothesis: The proportion of children successfully managed without specialist referral and without new dental caries will be higher in the test group compared with the control.

Aim 2. Develop a dental-specific health utility scale and measure the change in childhood health utility. Hypothesis: The change in health utility will be greater in the test group compared with the control.

Aim 3. Undertake an economic evaluation of the intervention. Hypothesis: The test intervention will have either less costs with greater/similar health gain or affordable incremental costs for additional unit of health outcomes.

Aim 4. Measure the change in childhood oral health-related quality of life. Hypothesis: The child oral health-related quality of life in the test group will be better than the control

Aim 5. Evaluate the acceptability of the ART-based care through focus group interviews. Hypothesis: The ART-based care will have greater acceptability than the control.

Methods

Study Design

We will undertake a two-arm parallel cluster randomized controlled study in which a test group will be provided with the intervention treatment at the start of the study and a control group will be provided the intervention treatment 12 months after study commencement (delayed intervention) in the Kimberley region of WA.

Ethics

Ethics approval for the study has been provided by the University of Adelaide, Human Research Ethics Committee (HREC) (Ethics approval No. H-2017-015), and the Western Australia Country Health Service HREC (Project Reference #2017/01) and the WA Aboriginal Health Ethics Committee (Project Reference #790).

Recruitment

We will adopt successful recruitment strategies applied in a wide body of research undertaken by author LJ in her work (unpublished) with Aboriginal communities in South Australia and the Northern Territory. This has included extensive engagement with Aboriginal communities and active community participation in the research process. We will engage with community elders through linkages established by authors DA and RM who both have a long association with Aboriginal communities in the Kimberley region. We will employ local Aboriginal people as research assistants to facilitate with community engagement and participant recruitment guided by a senior project officer based in Kimberley. Participant recruitment will be a two-step process: (1) elicit specific communities to participate, and (2) elicit individual participation. A Senior Research Officer appointed to coordinate the project

with the assistance of an Aboriginal research assistant will meet with the Chief Executive Officers of individual Aboriginal communities to explain the proposed study to invite community participation in the study. An Aboriginal Advisory Group with representation from all the Aboriginal Controlled Health Organisations in Kimberley will also be formed to provide appropriate guidance to the research team and assist with information dissemination and participant recruitment. Individual participant recruitment will use active engagement with community members at locations where study participants are likely to gather, such as visits to early childhood learning facilities, community general store, local community women's functions, and through word-of-mouth dissemination of project information. Parents and guardians will provide signed informed consent after being provided with information about the study and the processes undertaken to protect and preserve data confidentiality.

Parents and children aged 0-4 years, residing in selected communities in the Kimberley region of WA will be eligible. Children with complex medical conditions or developmental syndromes would be excluded. All other children within the scope for age and who consent to participate will be recruited.

Participating communities, stratified by size of community (ie, number of children in the sample frame) and baseline dental caries experience, will be randomly assigned using a computer-generated block randomized list into immediate (test group) or delayed intervention (control group, given standard care) by a central study coordinator. We will select communities for recruitment based on available information on community population from various sources (eg, Community CEOs, the

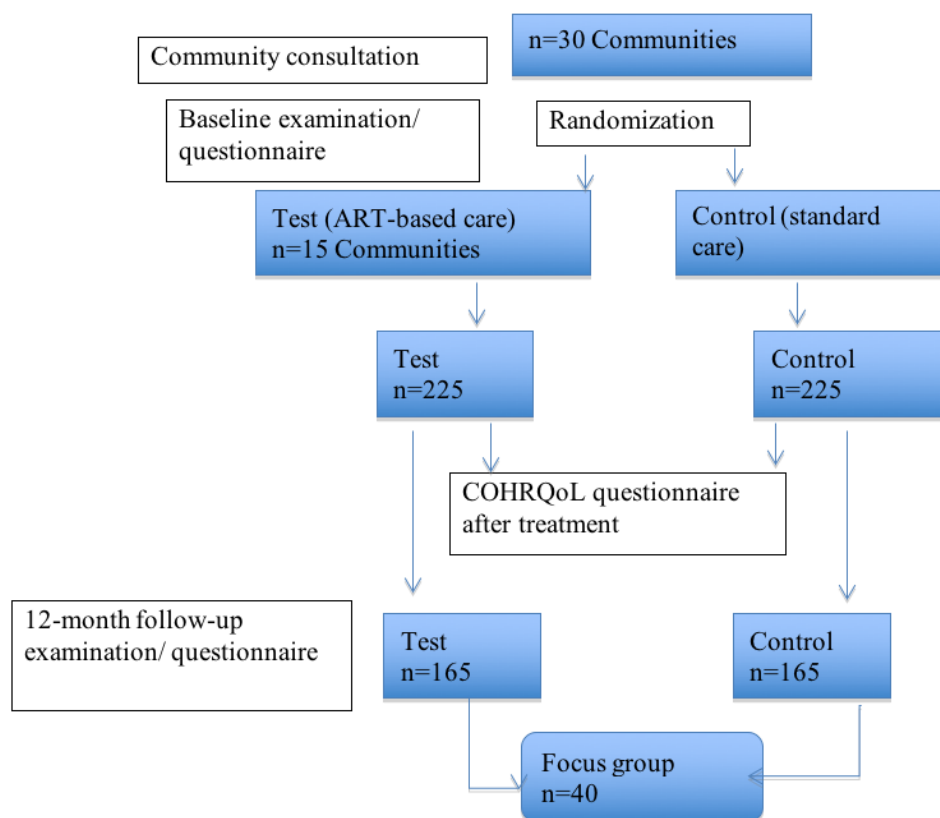
WA Country Health Service, Australian Bureau of Statistics). Communities will also be far enough apart to minimize contamination of test and control (at least 50 km). We will invite participation from communities with at least 100 people to ensure likelihood of recruiting at least 15 children in the age group of interest. We will stratify the communities on size of population and dental caries experience (high vs low; data obtained at baseline examination). Parents of all children of eligible age will be provided with information and consent forms and a questionnaire to complete (Aboriginal research assistants will explain the study to the parents and help parents complete the questionnaires). After receipt of signed consent, participants in the randomized study will be contacted for a baseline clinical examination by a calibrated examiner. After baseline examination, all participants will be contacted by the trial coordinator and appointments arranged for those allocated into the early treatment group. Test group participants will subsequently be contacted and appropriate appointments coordinated to be seen at the local SDS clinics or field clinic settings for treatment. Control group participants will be provided with standard preventive care by the Aboriginal Health Workers and managed for treatment as per standard procedures.

Study participants will be reviewed after 12 months from baseline and will undergo a clinical examination and complete a follow-up questionnaire. [Figure 1](#) shows the study's participant flow chart.

Outcomes

Primary outcomes are specialist referral and the increment in dental caries. Secondary outcomes are quality of life and acceptability of the ART-based care.

Figure 1. Participant flow chart.



Measures

Researchers will help the parents/caregivers complete a baseline questionnaire collecting information on COHRQoL using the Early Childhood Oral Health Impact Scale (ECOHIS) for children ≤ 6 years old [28]. The scale has been evaluated for Australian children and found to have acceptable reliability and validity [29]. We will also collect parent fear levels using the Index of Dental Fear and Anxiety [30] and child dental fear as reported by the parents as well as self-report by children ≥ 3 years old using the faces scale [31]. Changes in health utility will be evaluated using the generic Child Health Utility 9D Index (CHU_9D) [32], the Euroqol 5D Youth (EQ-5D-Y), and the new oral health specific utility scale planned to be developed in this study. The ECOHIS has been used successfully among Australian Aboriginal population by author LJ in her National Health and Medical Research Council (NHMRC) supported research on pregnant Aboriginal women, while the other measures have been used among disadvantaged populations. We will also evaluate the validity of the questionnaires used among this population.

Participant involvement in the proposed study is shown in Table 1. Both test and control groups will complete the same questionnaire on COHRQoL, child dental fear, the CHU_9D, and the EQ-5D-Y, one month after treatment. The test and control groups will also complete the childhood oral health related questionnaire and the CHU_9D and the EQ-5D-Y, at the one-month posttreatment, but anchoring their responses to what their child's oral health was like before the treatment ("Then-test") to evaluate the possible effects of response shift [33]. Questionnaires on COHRQoL and parent/child fear and anxiety will again be collected at the 12-month follow-up.

We anticipate the clinical examination to take about 10 minutes, and completion of the questionnaire about 30 minutes. ART-based treatment times will vary depending on the extent of treatment required. Treatments may involve multiple appointments, usually about 20 minutes at each appointment. A sample of study participants will be invited to focus group interviews, which will take approximately 1 hour per group.

All participants will also be clinically examined at the 12-month follow-up, by a "blind" calibrated examiner to evaluate their oral health status. Effectiveness will be assessed by the number of teeth treated, dental caries increment, and changes in quality of life. The quality of the treatment provided will be assessed

by blind calibrated examiners at follow-up, 12 months after treatment, using established criteria for determining ART restorations [34]. Clinical status of the teeth will be assessed using International Caries Detection and Assessment System-II criteria, which span the continuum from sound to extensive decay [35].

Economic Evaluations

Cost-Effectiveness Analysis

Cost-effectiveness of the intervention will be estimated using standard approaches [36] and will be from a health care provider perspective. Effectiveness measures will be the number of children managed in primary care without need for specialist referral, changes in COHRQoL, the numbers and types of treatments provided, and dental caries increments. The economic evaluation will compare any incremental costs of the intervention (ie, costs accrued in the intervention arm compared to those in the control arm) to the full list of incremental primary and secondary outcome endpoints, all expressed in their natural units of measurement. Costs will be measured from activity data with pathway analysis to fully specify all activities in both intervention and control arms. The resource use and dental services utilization will be obtained from research team records and intervention provider records. Measured resource use will be valued using both existing estimates of the costs of each unit of the resource use from market prices and the Dental Benefit Schedule fee rates for nonspecialist and specialist attendances. Standard discounting will be applied to both cost and outcomes. Uncertainty in the cost and outcome data will be subjected to sensitivity analyses.

Cost Utility Analysis

Cost-utility analysis will be undertaken using scores derived from the CHU_9D [37,38], the EQ-5D-Y, and the new oral health specific utility scale developed in this study. The use of scores from the CHU_9D as outcome measures in child dental health has been suggested [39]. However, in a preliminary evaluation as an outcome measure it was found not to be sensitive to changes in childhood oral health [40], while the use of the adult version of the EQ-5D has been suggested as being able to differentiate oral health states [41]. Hence, we will further test the usefulness of the CHU-9D as an outcome measure for childhood oral health and seek to develop an oral health specific multi-attribute utility instrument within this project.

Table 1. Participant involvement in the proposed study.

Timepoint	Intervention group (test)	Delayed intervention group (control)
Baseline	Questionnaire: ECOHIS, CHU_9D, EQ-5D-Y, Dental Utility Scale, dental fear and anxiety of parent and child; Clinical assessment of children; ART-based care	Questionnaire: ECOHIS, CHU_9D, EQ-5D-Y, Dental Utility Scale, dental fear and anxiety of parent and child; clinical assessment of children; standard care
1 month after baseline treatment	Questionnaire: ECOHIS, CHU_9D, EQ-5D-Y, Dental Utility Scale; child dental fear and anxiety	Questionnaire: ECOHIS, CHU_9D, EQ-5D-Y, Dental Utility Scale; child dental fear and anxiety
6 months after baseline treatment	ART-based care; focus group interviews	Standard care; focus group interviews
12 months after baseline treatment	Questionnaire: ECOHIS, CHU_9D, EQ-5D-Y, Dental Utility Scale; child dental fear and anxiety; clinical assessment	Questionnaire: ECOHIS, CHU_9D, EQ-5D-Y, Dental Utility Scale; child dental fear and anxiety; clinical assessment; ART-based care

Dental Specific Multi-Attribute Utility Instrument and a New Dental Utility Scale

We will use the available dataset of ECOHIS from the 250 respondents in the recently completed WA pilot study [29]. Although valid and widely used, available quality of life instruments in oral health cannot be used to measure quality-adjusted life years (QALYs). We will use the methodology described by Brazier and Rowen et al [42,43] to guide the development of the new oral health specific preference-based instrument. This includes a six-stage approach: establish dimensionality (Stage 1), eliminate and select items per dimension (Stage 2), explore item-level reduction (Stage 3), validate instruments (Stage 4), apply the new instrument to elicit health state values for a sample of health states described (Stage 5), and analyze the model results to produce utility values for all health states (Stage 6). The new Dental Utility Scale will then be developed.

This will be the first multi-attribute utility instrument in oral health conditions as well as the first validated multi-attribute utility instrument in this age group. This new instrument and its scale will be used to calculate QALYs for the cost-utility analysis.

Treatment Procedures

Test children will be provided with care by dental therapists previously trained in and using the ART approach. Treatment will be undertaken at SDS clinics or field settings, using portable equipment. Restorative treatments will be provided using hand instruments principally, without the use of local anesthesia with the cavity prepared and subsequently restored with a glass-ionomer cement. Where extractions are required, the procedure will be undertaken using standard care approaches. All children will also be provided with preventive fluoride varnish applications at treatment and reviewed at 6-month follow-ups. All treatment will be recorded in patient clinic records. At the 6-month reviews, participants will be provided with preventive fluoride varnish and any other necessary care. Children unable to be provided with care will be referred for specialist care. There will be no direct costs incurred by the participants for the primary care.

Control children will be provided with standard care as part of the fluoride varnish program. Children found to require dental treatment will be referred for care through the prevailing care pathway, that is, government dental services or local private practitioners.

In order to ensure all participants are offered the opportunity to access dental treatment, and in keeping with the delayed treatment intervention design, control participants will be offered treatment using the test treatment approach after the 12-month follow-up.

Focus Group

A sample of parents from the randomized test and control groups will be invited to participate in focus group interviews to elicit their perspectives on the care provided to their child using the various approaches (including those referred for GA care). Children will not be involved in the focus group interviews due to their young age. Previous experience with focus group interviews indicated that a sample of about 20 from each arm of the study is sufficient to reach saturation.

The focus group questions will be based on the following:

1. What were some of the positive aspects of dental care your child experienced?
2. What were some of the negative aspects of the dental care your child received?
3. Can you give some examples of what you think could have been done/implemented better during your child's treatment?
4. Can you name some aspects of the setting/location/process that you think could have been improved?
5. Can you identify any changes to your oral health knowledge since the research began?

Sample Size

A recently completed pilot study in WA, which compared ART-based care against standard care, reported a nine-fold difference in the proportion of children referred for specialist pediatric dentist care (5% vs 49%). A conservative difference in effect size of 2.5 was assumed to estimate the sample size (10% vs 25%). The intracluster correlation was estimated from the dental caries experience of Aboriginal children participating in a NHMRC Project Grant (1010758) funded cluster randomized trial (.05). Using these parameters, with 15 clusters available in each arm of the trial, the estimated sample size required, at 80% power and alpha of .05, was 165 in each arm of the trial with 11 children per cluster. Allowing for loss to follow-up of 25%, the estimated sample size is 220 per arm of the study or 15 children per cluster. The recently completed pilot trial in WA, undertaken by author PA, achieved 90% retention of study participants after 12 months, while an oral health promotion intervention undertaken by author LJ among an Aboriginal population achieved 80% retention of study participants. The estimated sample size will have sufficient power to detect a 33% difference in mean ECOHIS at 90% power and alpha of .05.

The study timeline is shown in Table 2. It is expected that community engagement will take the bulk of the first year in recognition of the challenges of undertaking research in northwestern WA, which is as far as Sydney is from Perth (about 3000 km). Participant recruitment and treatment provision is similarly expected to take up to 2 years because of constraints of locations of communities and weather conditions.

Table 2. Study timeline, indicated by actions taken per quarter.

Action	Year 1				Year 2				Year 3				Year 4				Year 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Community engagement, staff recruitment, training, ethics approval, printing	✓	✓	✓	✓																
Participant recruitment, baseline, examinations, randomization, commence treatment, baseline data entry			✓	✓	✓	✓	✓	✓	✓	✓										
Follow-up examinations, focus group interviews, delayed intervention group treatments									✓	✓	✓	✓	✓	✓	✓	✓				
Data entry, data clean-up, data analyses											✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Report preparation, community presentation and feedback																			✓	✓

Data Analysis

Data will be analyzed on an intention-to-treat (ie, participants analyzed on the basis of their group allocation regardless of whether they received the intended treatment), and per protocol basis (participants analyzed on the basis of their group allocation and receiving the intended treatment). Descriptive statistics will be presented and baseline variables will be compared between groups to test for fairness with respect to the randomization. Aim one (primary outcome) will be tested using test of proportions and logistic regression to control for potentially confounding factors. Changes in health utility and COHRQoL (secondary outcomes) will be tested using paired (within group) and unpaired (between groups) and parametric and nonparametric tests as appropriate, and multivariate analysis using linear regression for continuous variables and Poisson regression for count variables to control for possible intergroup imbalances. Responsiveness of the COHRQoL scale will be determined by calculation of effect sizes for the scale overall and specific domains. Statistical significance will be set at $\alpha=0.05$. All analyses will take into account the cluster design and will incorporate multilevel analyses where indicated. Multiple imputation of missing data will be further undertaken to evaluate its impact on the primary and secondary outcomes.

Qualitative Analysis

NVivo9 computer software will be used to code the transcripts from the focus groups. Emergent themes from the focus groups will then be explored ($n=20$ from each arm). Transparent validation of emergent themes and content will be performed using 2 coders. Thematic analysis will be performed as such an approach allows for contextual differences between perceptions, experiences, and belief to be developed and explored.

Incremental cost-effectiveness ratio—the ratio of incremental costs to incremental outcome between the test and control group—will be calculated. Incremental outcomes for the cost-effectiveness analysis include differences in number of children treated in primary care settings without the need for specialist pediatric dental referral, the differences in COHRQoL between and within groups, the differences in number and type of treatment provided, re-treatment, and antibiotics for dental infections over the 12-month period. Incremental outcome for cost-utility analysis refers to difference in health utility scale.

Data Quality Control

Hard copy data will be entered electronically into a database software, and data will be checked at entry. The database will have data validation parameters incorporated to alert for any values that are outside of permissible values. Participants will be contacted to clarify and amend ambiguous or confusing responses. Data cleaning will be undertaken with 2 people, one to scan the data entry and the other to verify from the hard copy.

Results

Community consultations have been undertaken, and 26 communities have agreed to participate. Fieldwork is in progress to recruit study participants.

Discussion

Principal Considerations

Closing the gap in Aboriginal child health is a national priority. A lack of access to dental services by rural and remote Aboriginal communities has been highlighted. The outcomes of the proposed study will address multiple goals of the NHMRC 2013-15 strategic plan, primarily to “improve the health of Aboriginal peoples and Torres Strait Islanders through the support of health research and its translation”. The research team, comprising established oral health researchers and child health researchers working in Aboriginal health, community development, health economists, dental practitioners, and oral health policy makers, will ensure that the findings of the study can be readily translated into policy and practice. Second, the research is driven by provision of care at the primary care level and will test the capacity of the intervention to reduce the need for tertiary care at hospital for a condition that is essentially a preventable hospital admission and to reduce health inequalities. Third, our research proposal supports the NHMRC goal of “healthy start for healthy life” by engaging with Aboriginal families in the provision of dental care by offering treatment and preventive services.

The outcomes will have a direct impact on the COHRQoL for the study participants because all participants in the treatment arms will be provided with an opportunity to receive dental treatment. The research will also have flow-on effects through the demonstration of a model of care with potential applications in other settings throughout Australia, such as aged care facilities

and nursing homes and among population with disabilities/special needs. The study also addresses the oral health needs of priority populations identified in the Australian National Oral Health Plan, 2015-2024, specifically, Aboriginal and Torres Strait Islander people. It will also have impacts for other priority populations identified in the National Oral Health Plan, namely, people who are socially disadvantaged or on low incomes, and people living in regional and remote areas.

We will further undertake oral health promotion and community development to ensure sustainability of the oral health promotion activities by engagement with the Aboriginal Communities and community champions. Furthermore, the development of a condition specific health utility scale will be a major advancement in enabling economic evaluation of oral health care programs for young children using a preference-based measure.

We will also employ Aboriginal research assistants who will be trained in dental clinic assisting as well as research processes.

They will also participate in the oral health promotion activities and in the process will be trained to undertake community oral health promotion activities, which will add to capability development within Aboriginal communities. We will also disseminate the study findings to the participating communities by holding community forums as well as ad hoc sit-down chats to present study findings and will meet with the Chief Executive Officers of the Aboriginal Communities to report on the study findings as well as provide them with a written report.

Conclusion

The significance of this study lies in its holistic approach to testing the model of care. Clinical evaluations as well as oral health related quality of life evaluations will be undertaken. Cost-effectiveness and cost-utility evaluations will assist in the development of policy options for oral health services for rural and remote communities. The elicitation of caregiver perspectives through focus group interviews will supplement the clinical, psychosocial, and cost-utility evaluations and provide a richer evaluation of the intervention.

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Conflicts of Interest

None declared.

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Abbreviations

ART: atraumatic restorative treatment
CHU_9D: Child Health Utility 9D Index
COHRQoL: child oral health-related quality of life
ECC: early childhood caries
ECOHIS: Early Childhood Oral Health Impact Scale
EQ-5D-Y: Euroqol 5D Youth
GA: general anesthesia
HREC: human research ethics committee
NHMRC: National Health and Medical Research Council
QALYs: quality-adjusted life years
SDS: School Dental Service
WA: Western Australia

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Protocol

Patient Preferences and Willingness to Pay for Cervical Cancer Prevention in Zambia: Protocol for a Multi-Cohort Discrete Choice Experiment

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Abstract

Background: Although most countries in southern Africa have cervical cancer screening programs, these programs generally fail to reach a significant majority of women because they are often implemented as pilot or research projects, and this limits their scope and ability to scale up screening. Some countries have planned larger-scale programs, but these have either never been implemented or have not been successfully scaled up. Most of the global burden of cervical cancer is experienced in countries with limited resources, and mortality from cervical cancer is the most common cause of cancer-related deaths among women in Sub-Saharan Africa.

Objective: The purpose of this study is to learn about preferences for cervical cancer screening in Zambia, to identify barriers and facilitators for screening uptake, and to evaluate willingness to pay for screening services to support the scaling up of cervical cancer screening programs.

Methods: We will conduct a discrete choice experiment by interviewing women and men and asking them to choose among constructed scenarios with varying combinations of attributes relevant to cervical cancer screening. To inform the discrete choice experiment, we will conduct focus groups and interviews about general knowledge and attitudes about cervical screening, perception about the availability of screening, stigma associated with cancer and HIV, and payment for health care services. For the discrete choice experiment, we will have a maximum design of 120 choice sets divided into 15 sets of 8 tasks each with a sample size of 320–400 respondents. We will use a hierarchical Bayesian estimation procedure to assess attributes at the following two levels: group and individual levels.

Results: The model will generate preferences for attributes to assess the most important features and allow for the assessment of differences among cohorts. We will conduct policy simulations reflecting potential changes in the attributes of the screening facilities and calculate the projected changes in preference for choosing to undergo cervical cancer screening. The findings from the discrete choice experiment will be supplemented with interviews, focus groups, and patient surveys to ensure a comprehensive and context-based interpretation of the results.

Conclusions: Because willingness to pay for cervical cancer screening has not been previously assessed, this will be a unique and important contribution to the literature. This study will take into account the high HIV prevalence in Sub-Saharan Africa and prevailing gender attitudes to identify an optimal package of interventions to reduce cervical cancer incidence. This simulation

of women's decisions (and men's support) to undergo screening will lay the foundation for understanding the stated preferences and willingness to pay to help design future screening programs.

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KEYWORDS

discrete choice experiment; cervical cancer prevention; economic evaluation

Introduction

Around the world, a woman dies of cervical cancer about every 2 minutes [1], with 528,000 new cases and 266,000 deaths in 2012. Cervical cancer affects women during their most productive years because the majority are diagnosed under the age of 50; therefore, cervical cancer adversely affects not only women but also their families [2]. A large proportion of the global burden is experienced in countries with limited resources, and mortality from cervical cancer is the most common cause of cancer-related deaths among women in Sub-Saharan Africa [3,4]. The high prevalence of HIV in Sub-Saharan Africa, the focal point of the HIV/AIDS epidemic, makes the cervical cancer burden even more acute in these countries because women with HIV have a much higher incidence rate of cervical cancer than uninfected women [5]. Fortunately, given the advances in HIV/AIDS treatment in Sub-Saharan Africa, women are living longer with HIV, but unfortunately, they are dying from cervical cancer due to the scarcity of large-scale implementation of screening programs.

Cervical cancer is preventable, and early diagnosis is possible using low-cost technologies [6]. The World Health Organization guidelines recommend several screening approaches, including tests for human papillomavirus (HPV) and cytology (Pap test) and visual inspection with acetic acid (VIA) [7]. The screen-and-treat approach using VIA or low-cost rapid HPV test is the favored approach in the limited resource setting because it minimizes loss to follow-up [8]. Therefore, the knowledge and technology base exists to prevent and screen for cervical cancer in low-resource settings and, as in other settings, large-scale sustainable screening programs can be implemented [9-11].

Although most countries in southern Africa have a cervical cancer screening program that is either administered by the government or nongovernmental organizations, these programs generally fail to reach a significant majority of women [12]. This is largely because most screening activities in southern Africa are part of pilot or research projects, which limits their scope and ability to scale up screening. Some countries have planned larger-scale programs, but these have either never been implemented or have not been successfully scaled up. For example, Malawi attempted a nationwide cytology-based cervical cancer screening program, but it quickly deteriorated owing to lack of resources, trained professionals, and infrastructure [13].

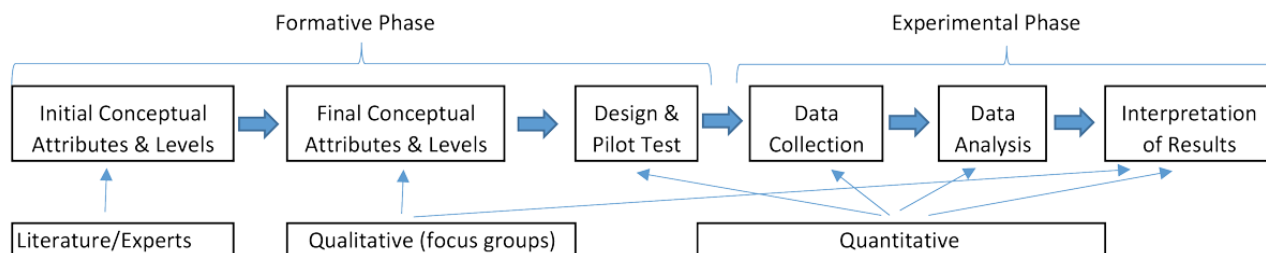
Therefore, there is an urgent need to implement low-cost approaches already available for the prevention and early detection of cervical cancer in Sub-Saharan Africa. However, to date, no study has systematically evaluated preferences for prevention and screening, and this information is required to design and implement programs that will result in optimal uptake. Additionally, the financing of prevention and screening services is a significant barrier for scale-up.

Although discrete choice experiments (DCEs) have been performed in the context of maternal and child health, health infrastructure, and workforce development in Africa [14-16], no study has used validated quantitative methods to evaluate the willingness to pay for cervical cancer screening in Africa. Fee contributions based on an individual's ability to pay, with safeguards for ensuring free access for the disadvantaged population, can provide a continuous, even if small, stream of revenue to allow for the sustainability of program operations. In this study, we will use DCE to elicit preferences for cervical cancer screening to identify barriers and facilitators for screening uptake and evaluate the willingness to pay for screening services, which can inform innovative financing arrangements to ensure sustainability. This study will be conducted in Zambia, one of the countries with the highest burden of cervical cancer in Sub-Saharan Africa.

Methods

Framework for Designing and Conducting the Discrete Choice Experiments

In this study, women and men or partners of eligible women will be asked to choose among constructed scenarios with varying combinations of key attributes relevant to cervical cancer screening (for example, type of provider, cost, and distance to facility); choosing to have no screening will also be an option. The DCE approach is preferred over asking women and men about their willingness to pay directly in surveys or interviews [17-19]. DCE allows participants to choose among scenario combinations, an approach which provides them with a more natural consumer choice experience. Figure 1 provides an overview of the mixed-methods approach for implementing DCE. We will begin by identifying initial concepts and attributing levels for DCE based on feedback from experts and a review of the literature related to cervical cancer screening barriers and facilitators. Next, we will conduct a series of focus groups and interviews with stakeholders in Zambia to finalize the attributes and levels.

Figure 1. Mixed-methods framework for the discrete choice experiment.

Focus Groups and In-Depth Interviews

We will conduct two sets of focus groups with women and interviews with a range of stakeholders including women and men who are between the ages of 25 and 49 years. We plan to interview at least 8 individuals in each of the following groups: women who are HIV-negative, those who are HIV-positive, those who have been diagnosed with precancerous lesions, and those treated for cancer.

We will also interview men in both urban and rural locations. The focus groups and interviews will not address personal issues but will be directed at understanding general knowledge and attitudes about cervical screening, perception about the availability of screening, stigma associated with cancer and HIV, and payment for health care services. Written consent will be obtained from all participants, and the consent form will be translated into the local languages of Bemba, Nyanja, and Tonga. We will also interview providers to gain knowledge about the delivery of health care services, the use of cervical cancer screenings, and facilitators and barriers related to cervical cancer screening, diagnosis, and treatment. The key objective of these discussions is to gain insight to finalize the attributes and corresponding levels for DCE.

We will use a structured data collection template for standardization and coding to facilitate analysis. We will combine the qualitative information from all stakeholders to assess convergence around common themes and identify potential differences in viewpoints expressed by participants on specific topics. The prespecified coding scheme (refined as needed) will be used to perform a comparative assessment of barriers and facilitators, program attributes, and financing options. To assist in interpreting the findings, we will visually display the data in tabular and graphical formats.

Discrete Choice Experiments Graphics, Choice Set Selection, and Supplementary Survey

To permit use in a low-literacy environment, the attributes and levels will be converted into graphics (see example of the attributes and levels and the graphics provided in [Table 1](#) and [Figure 2](#)). Our DCE selection ([Table 1](#)) will generate 200 possible scenarios ($5^2 \times 2^3$), which are too many for any single respondent to assess. To select a fractional set of scenarios, we will employ a randomized design process that ensures that respondents see well-balanced and near-orthogonal fractions of the full-choice design (8 choice decisions per respondent). We will have no more than 128 profiles that will need to be tested after developing the fractional set of scenarios. Wong et al reported that even 729 possible profiles can be reduced to 128

profiles with a fractional factorial design [20]. In addition to the choice tasks, we will administer a supplemental survey to obtain demographics, socioeconomic status, reproductive history (women only), cervical cancer screening knowledge and use (women only), HIV status, access to care, attitudes toward using formal medical care (compared with traditional medicine), and stigma associated with HIV and cancer diagnosis.

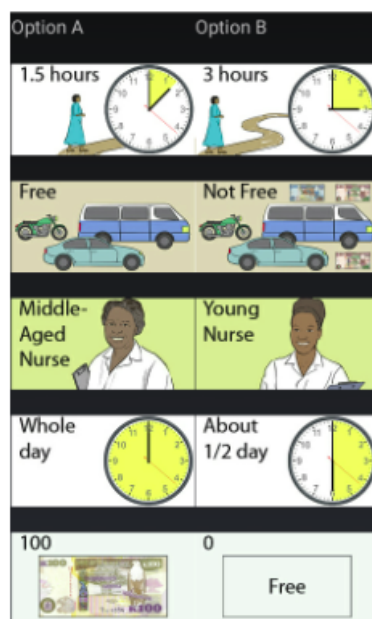
Cohort Selection and Sample Size

A key design consideration for DCE is to allow for both group-level and individual-level differences. The key groups of interest are HIV-positive women, HIV-negative women, women with unknown HIV status, and men (male partners). In addition, it is important to distinguish between urban and rural cohorts because they can differ in terms of participant attitudes, cultural sensitivities, and health care infrastructure. Finally, to also capture health-seeking behavior and potential underlying differences between those who attend health clinics and those who do not (owing to stigma, religion, traditional beliefs, cost, and other reasons) [21], we also will draw specific cohorts from health clinics and another set of cohorts from the wider community. We describe the 7 cohorts targeted for DCE in [Textbox 1](#).

Sample size calculation for DCE studies in health care is an evolving field. Johnson et al simulated sample sizes to estimate precision that could be obtained for DCE studies [22]. They found that precision increases rapidly at lower sample sizes (less than 150 observations) and then flattens out at around 300 observations. Based on this, the rule of thumb for DCEs is that generally 300-400 cases per group are adequate. Hall et al and Lancsar and Louviere have indicated that about 20-25 respondents per choice set can provide precise parameter estimates [23,24]. Our proposed study, with a maximum design of 120 choice sets that will be divided into 15 sets of 8 tasks each, can achieve this with a sample size of 320 to 400. Another approach recommended by Johnson and Orme [25] suggests that the sample size required for the main effects depends on the number of choice tasks (t), the number of alternatives (a), and the number of analysis cells (c) according to the following equation: $N > 500c/(t \times a)$. When considering the main effects, c is equal to the largest number of levels for any of the attributes. For our proposed model, the values are $t=8$, $a=2$ (without option to select neither choice), and $c=5$ (main effects) or $c=10$ (based on planned interaction between 5-level and 2-level attributes); therefore, for the main effects, N can be estimated as $(500 \times 5)/(8 \times 2) = 156.25$ observations and for effects with interactions, N can be estimated as $(500 \times 10)/(8 \times 2) = 312.50$ observations.

Table 1. Attributes and levels for the discrete choice experiment.

Attribute	Level
Distance (hours by foot)	1, 1½, 2, 2½, 3
Transport	Free; not free
Provider	Middle-aged nurse; young nurse
Wait time	About half a day; full day
Cost (in Zambian kwacha)	0, 25, 50, 75, 100

Figure 2. Discrete choice experiment: example graphics.

Textbox 1. Study cohorts for the discrete choice experiment. For each of the 7 groups, 400 individuals were selected. A previously conducted pilot test included 15 women and 15 men.

1. **Health clinic cohort**

- HIV-positive women
- HIV-negative and unknown women
- Men (male partners of women when possible)

2. **Community cohort**

- Urban women
- Urban men
- Rural women
- Rural men

3. **Justification for cohort selection**

- Health clinic: To systematically identify HIV-positive women; women who attend clinics may also differ from the general population (owing to stigma, traditional beliefs, cost, etc).
- Community: To understand screening preferences from cohorts that are most likely to reflect the general population.

In all the approaches identified above, a sample size of 400 per group will be adequate to perform DCE to obtain preferences and willingness to pay estimates for each of the 7 targeted

cohorts. Therefore, we will include a total sample of 2800 individuals.

Identifying Discrete Choice Experiments Participants

Two health clinics that treat middle- and low-income individuals in the Lusaka area will be randomly selected for the study; the government operates multiple community-based clinics that offer a similar set of services to our target cohort and, therefore, we will be able to select a representative group of participants. The study interviewers (recruited based on experience performing similar studies) will visit the health centers to recruit participants on a continuous basis by inviting eligible women and men to complete the survey. Written consent will be obtained, and the survey will be conducted in an allocated room at the health center. For the community cohorts, we will identify respondents in Lusaka (urban) and appropriate rural or semirural setting. The interviews will take place at the residence of the participant or at a nearby community center.

Discrete Choice Experiments Data Collection Process

We will train a team of 4 interviewers (fluent in English and one of the other local languages) and a supervisor, who will be responsible for the data collection. The graphics and software created by RTI International (Research Triangle Park, North Carolina, USA) will be loaded onto tablets to allow easy manipulation and viewing by the respondent. The supplemental survey and data collection pertaining to the DCE choices will be entered directly into the tablet by the interviewer with quality control features to ensure accuracy of data input formats (dates, ages, and completeness of responses to questions). We will pilot-test the data collection process with 30 women and men (15 each) selected to reflect the targeted cohorts from Lusaka and rural districts. We will introduce all respondents to the graphics by presenting each illustration separately and explaining the attribute and level in detail. Each participant will become acquainted with the DCE approach through three warm-up example choice decisions prior to the presentation of the selected tradeoffs for that participant. After presenting the DCE choices, the interviewer will verbally pose the survey questions and record answers in the preformatted data collection tool (approximately 45 minutes will be required for the interviews). Respondents will be interviewed by one of the 4 trained interviewers or coordinator or supervisor as needed. The data will be reviewed on a daily basis by the supervisor for quality control (so that any issues identified can be quickly rectified) and uploaded as soon as possible into a central deidentified database that will be password-protected.

Discrete Choice Experiments Data Analysis and Interpretation

A hierarchical Bayesian estimation procedure will be used to assess attributes at the group and individual levels. Hierarchical regressions simultaneously assess relationships within a given level and between or across levels. This technique allows for independent variance to be calculated for both levels simultaneously. The model will generate preferences for attributes to assess the most important features and also allow for the assessment of differences among cohorts (eg, HIV-positive women vs others). We will conduct policy simulations reflecting potential changes in the attributes of the

screening facilities and calculate the projected changes in preference for selecting to undergo cervical cancer screening. The findings from DCE will be supplemented with information gained from other qualitative (interviews and focus groups) and quantitative (patient supplemental survey) data collection to ensure a comprehensive and context-based interpretation of the results.

This study has received ethical approval from the Institutional Review Boards at RTI International and the University of Zambia's Biomedical Research Ethics Committee. In addition, the Zambian Ministry of Health has reviewed and approved this study.

Availability of Data and Material

We will abide by National Institutes of Health policies and make the data from this study available to other researchers.

Results

The project was funded in July 2016 and ethical approval was obtained for the discrete choice experiment in April 2017. Enrolment is currently ongoing and we plan to complete data collection by August 2018. First results are expected to be submitted for publication in 2019.

Discussion

Because willingness to pay for cervical cancer screening has not been previously assessed, this will be a unique and important contribution to the literature. Sub-Saharan African countries have faced challenges in scaling up cervical cancer screening, and the ability to finance these programs has been one key barrier. This study, by addressing stakeholder preferences across key stakeholders as well as HIV-negative and -positive women and men, will take into account the high HIV prevalence in Sub-Saharan Africa and prevailing gender attitudes to identify an optimal package of interventions to reduce cervical cancer incidence.

Although DCE is a useful approach to elicit tradeoffs and choices, this experiment may not be able to account for all the contextual and institutional factors that affect actual behavior, especially given the complex nature of health care decision making. We will use the additional qualitative and quantitative information collected during the DCE implementation and incorporate background contextual aspects in reaching conclusions based on the DCE results. Despite the potential limitations of DCEs, this simulation of women's decisions (and men's support) to undergo screening will lay the foundation for understanding the stated preferences and willingness to pay to help design future screening programs. A more systematic national implementation process that is evidence-based, data-driven, and resource-based is required for long-term sustainable cancer control. The establishment of screening programs in high income countries have resulted in dramatic decreases in the incidence of cervical cancer [10,11], and with better implementation of tailored programs in Sub-Saharan, a similar decline can be achieved.

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Authors' Contributions

SS conceptualized the study; collected and analyzed data; wrote, reviewed, and edited the original draft; and administered the project. YK conceptualized the study and reviewed and edited the manuscript. YZ conceptualized; collected and analyzed the data; and reviewed and edited the manuscript. SH collected and analyzed the data; wrote, reviewed, and edited the manuscript; and administered the project. NN collected and analyzed the data; wrote, reviewed, and edited the manuscript; and administered the project. LP reviewed and edited the manuscript and administered the project. CC reviewed and edited the manuscript and administered the project. SK reviewed and edited the manuscript. GP reviewed and edited the manuscript and administered the project. All authors have provided their consent for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer-reviewer report.

[[PDF File \(Adobe PDF File\), 130KB - resprot_v7i7e10429_app1.pdf](#)]

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Abbreviations

DCE: discrete choice experiment

VIA: visual inspection with acetic acid

HPV: human papillomavirus

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Protocol

Using eHealth to Reach Black and Hispanic Men Who Have Sex With Men Regarding Treatment as Prevention and Preexposure Prophylaxis: Protocol for a Small Randomized Controlled Trial

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Abstract

Background: Black and Hispanic men who have sex with men in the United States continue to be disproportionately affected by HIV and AIDS. Uptake of and knowledge about biobehavioral HIV prevention approaches, such as treatment as prevention and preexposure prophylaxis, are especially low in these populations. eHealth campaigns and social media messaging about treatment as prevention and preexposure prophylaxis may help to fill this gap in knowledge and lead to increased uptake of such strategies; however, no evidence exists of the effects of these targeted forms of communication on treatment as prevention and preexposure prophylaxis uptake in these populations.

Objective: We describe the protocol for a 3-part study aiming to develop and evaluate an eHealth intervention with information about treatment as prevention and preexposure prophylaxis for HIV-positive and HIV-negative black and Hispanic men who have sex with men.

Methods: Phases 1 and 2 will involve focus groups and cognitive interviews with members of the target populations, which we will use to create a culturally tailored, interactive website and applicable social media messaging for these men. Phase 3 will be a small randomized controlled trial of the eHealth intervention, in which participants will receive guided social media messages plus the newly developed website (active arm) or the website alone (control arm), with assessments at baseline and 6 months.

Results: Participant recruitment began in August 2017 and will end in August 2020.

Conclusions: Public health interventions are greatly needed to increase knowledge about and uptake of biobehavioral HIV prevention strategies such as treatment as prevention and preexposure prophylaxis among black and Hispanic men who have sex with men. eHealth communication campaigns offer a strategy for engaging these populations in health communication about biobehavioral HIV prevention.

Trial Registration: ClinicalTrials.gov NCT03404531; <https://www.clinicaltrials.gov/ct2/show/NCT03404531> (Archived by WebCite at <http://www.webcitation.org/70myofp0R>).

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KEYWORDS

pre-exposure prophylaxis; treatment as prevention; men who have sex with men; eHealth; blacks; African Americans; Hispanic Americans; Latinos; HIV; social media; sexual and gender minorities; telemedicine; acquired immunodeficiency syndrome

Introduction

Background

There were an estimated 973,846 people living with HIV in the United States as of 2015; the US Centers for Disease Control and Prevention (CDC) further estimated that roughly 38,500 new infections occur annually [1]. Men who have sex with men (MSM) accounted for about 70% of those new infections in 2015, despite constituting just 2% of the country's population [2]. Moreover, roughly 70% of the new diagnoses that year were in black and Hispanic MSM [2].

Black and Hispanic MSM continue to be disproportionately affected by HIV/AIDS in the United States. These racial and ethnic disparities in HIV/AIDS rates are also apparent in the Providence, Rhode Island Metropolitan Area, where new HIV/AIDS diagnoses among MSM increased between 2007 and 2011 even as total new diagnoses declined [3]. Moreover, 30% of individuals with a new diagnosis in Rhode Island from 2009 to 2013 also presented with AIDS, with MSM status being the leading risk factor, suggesting that a significant number of MSM in Rhode Island are only reaching care late in the course of their disease [3].

Effective biobehavioral interventions for HIV prevention in such high-risk populations include treatment as prevention (TasP) and preexposure prophylaxis (PrEP). TasP refers to the use of antiretroviral treatment to decrease the risk of HIV transmission between serodiscordant partners by reducing the viral load in the infected individual's fluids to very low levels. TasP has been shown to have the potential to reduce HIV transmission to the partner without HIV by more than 96% [4]. PrEP is the daily ingestion of an oral single-tablet combination antiretroviral treatment by HIV-uninfected individuals. PrEP has been shown to have a greater than 90% chance of preventing HIV acquisition in adherent individuals, as confirmed by multiple studies [5-9]. However, knowledge about and uptake of PrEP and TasP remain low among black and Hispanic MSM [10,11]. Though results vary across studies, PrEP uptake is estimated at just 9.8% for black MSM and 6.6% for Hispanic MSM [12]. Barriers to PrEP uptake identified by previous research include lack of cultural competency in public health initiatives, stigma related to homosexuality and HIV serostatus, lack of targeted internet outreach, and low health literacy in the target populations [13].

One highly promising strategy to increase awareness, knowledge, behavioral intentions, and potential uptake of public health interventions that is underused in this context is eHealth, which refers to the use of a range of electronic technologies (eg, online social networking sites and apps, YouTube, and interactive websites) to provide health information [14-17]. eHealth has recently moved to the forefront of health communication because of its cost effectiveness, high levels of accessibility and acceptability in many populations, and effectiveness in previous public health campaigns [16,18-22].

Of all American adults, 84% use the internet [23] and MSM of all racial and ethnic groups have been found to have high rates of participation on online social media sites [24]. Recent research found that MSM frequently prefer information about HIV prevention (eg, PrEP) to be disseminated in electronic forms such as email and websites [21]. However, our recent review of the published literature did not find that any evaluations of health interventions using social media increased TasP or PrEP uptake in these high-risk populations, demonstrating its novelty.

Further, cultural tailoring, or the use of targeted messages for certain populations on the basis of known subgroup differences, has also been found to increase efficacy compared with generic health messaging [25,26]. For example, Kreuter and colleagues used messages to prompt African American women to increase their rates of mammography and healthy food consumption by tailoring those behavioral changes toward values such as religiosity, collectivism, and racial pride [26]. Yet few existing websites or online sources of HIV prevention information are tailored to black and Hispanic MSM. In addition, data on eHealth, and particularly social media's utility for minority populations, remain limited.

Objective

We describe the protocol of a 3-part study aiming to develop and evaluate an eHealth intervention with information about TasP and PrEP for HIV-positive and HIV-negative black and Hispanic MSM. One part of this project will involve the creation of a culturally tailored, interactive website for these men in the Providence Metropolitan Area and of similarly tailored social media messaging to promote the website and prompt participants to access it. The population-specific content and all aspects of the website and messages will be based heavily on data gathered from members of the population in the initial 2 phases of the study. The messages will also be grounded in the information-motivation-behavioral skills (IMB) and social cognitive theory (SCT) frameworks, which are widely accepted evidence-based approaches for promoting behavioral changes related to HIV risk reduction [27-32]. We hypothesize that using theory-based and culturally relevant social media messages will increase knowledge of TasP and PrEP among black and Hispanic MSM, positively affect their attitudes and behavioral intentions toward the interventions, and ultimately increase uptake. The overall objective of this study is to improve HIV prevention strategies among high-risk minority MSM through novel use of eHealth.

Methods

Study Design

This will be a 3-part study that includes focus groups and cognitive interviews to develop an eHealth intervention for HIV-positive and HIV-negative black and Hispanic MSM, and a small randomized controlled trial (RCT) to evaluate that

intervention. In phase 1, we will use 4 to 6 focus groups of 5 to 8 participants each to learn about TasP, PrEP, and social media use in the target population, as well as obtaining feedback on an existing interactive website (Men2MenRI [33]). Members of our team previously developed the website targeting white MSM in Rhode Island. Phase 2 will use cognitive interviews with 8 participants and an open pilot with 16 participants to develop and assess the acceptability of IMB- and SCT-grounded social media message content designed to motivate and encourage access to our newly developed website. In phase 3, we will conduct a small RCT (n=100 participants, with 50 in each arm) comparing the combination of sending social media messages plus the website (active arm) versus the website alone (control arm). Study materials (eg, recruitment flyers, interview guides, questionnaires, website, and social media messages) and findings (eg, qualitative and quantitative data) will also be assessed by a community advisory board made up of 6 to 12 members from the local community who reflect the target groups. The study is approved by the Brown University Institutional Review Board (#1612001661), Providence, Rhode Island, USA, and the US National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention's project determination process. This study is also registered on ClinicalTrials.gov (NCT03404531).

Participant Recruitment

Participants will be HIV-positive and HIV-negative black and Hispanic MSM who are 18 years of age and older living or working in the Providence Metropolitan Area (all of Rhode Island and Bristol County, Massachusetts). Participants must also fit the CDC definition of high risk—that is, have engaged in condomless anal intercourse within the past 6 months; be biologically male and identify as male; and be able to give written informed consent in English or Spanish. For phase 3, participants must also report not taking PrEP if they are HIV-negative, or in HIV care or taking treatment if they are HIV-positive, at the time of enrollment in the study. We will recruit participants for all phases of the study using a variety of methods, including advertisements online and on public transportation; posted signs and flyers in local community and commercial venues; and in-person outreach at places where the target population congregates, such as community-based organizations, clinics, bars, and clubs. Individuals interested in participating will be screened for eligibility over the phone using the aforementioned criteria. Participants will provide written informed consent prior to participating in the focus group, cognitive interview, or baseline assessment.

Procedures and Interventions

For all phases, participants will complete a demographics form at the time of their enrollment. For phase 1, we will attempt to stratify the groups by race/ethnicity (black vs Hispanic) and HIV serostatus (HIV-positive vs HIV-negative). Focus groups will be facilitated by 2 trained staff members in English or Spanish using a semistructured discussion guide and will last roughly 2 hours. In both parts of phase 2, we will attempt to have a balance of participants from each of the 4 categories from phase 1 (black HIV-negative, Hispanic HIV-negative, black HIV-positive, and Hispanic HIV-positive). The cognitive

interviews will be 2- to 3-hour sessions in English or Spanish using a semistructured interview guide with open-ended questions, also administered by a trained member of the research team. All phase 1 focus groups and phase 2 interviews will be digitally recorded and professionally transcribed. For the open pilot portion of phase 2, participants will attend an individual information session at the study location, where they will be provided with a broad description of the intervention and view the website. They will then participate in the newly developed intervention (website plus messages) for 1 week. Lastly, participants will return to the study location to complete a brief (1-hour) individual in-depth interview about the website and messages. Based on the feedback we receive during these interviews, we will alter intervention materials and procedures prior to the implementation of the study as a small RCT during phase 3.

We will randomly assign phase 3 participants to have access to either the website with social media messages (intervention condition) or the website alone (control condition). Participants will be stratified by race/ethnicity and HIV serostatus as in phases 1 and 2. We will use block random assignment in batches of 10, by HIV status and race/ethnicity, to keep the sizes of the intervention or comparison groups similar. Participants will physically come to the study site at enrollment for study description, consent procedures, website demonstration, randomization, demographic and HIV treatment and prevention history information collection, and baseline assessment; then they will come again 6 months later for the follow-up assessment. Participants will be assigned a research identification number, which will be used for all data collected to ensure confidentiality. Participants will be compensated in cash (all in US \$) \$40 for the focus group, \$50 for the cognitive interview, \$35 for the open pilot, and \$80 for the small RCT (\$40 for the baseline assessment and \$40 for the 6-month follow-up) plus a potential \$10 for transportation or child care costs incurred to attend study sessions. Eligible individuals will be allowed to participate in only 1 phase of the study.

Each phase of the study will provide unique information that will then inform the following phases. We will use focus group data from phase 1, which will include gathering feedback on the existing Men2MenRI website and to learn about TasP, PrEP, and social media use in the target populations, to create our new website and social media messages in a way that is audience specific. We will then use cognitive interviewing in phase 2 to further refine and develop the website and messages to be tailored to participant serostatus and race/ethnicity. Lastly, we will conduct an open pilot to evaluate and improve study procedures prior to the implementation of the small RCT in phase 3.

Measures

Phases 1 and 2 measures will involve using qualitative interview guides, informed by the extant literature and developed by the team, to identify important themes in the data. For phase 3, participants will complete the study assessment at enrollment (baseline) and at a 6-month follow-up, which will be digitally administered using iPads. The assessment will include self-report questions about HIV testing history, date(s) of

previous testing, source(s) of previous testing, viral load, CD4 count, linkage and retention in care, TasP uptake, HIV medication, adherence and viral load if HIV-positive, and consideration of PrEP, including barriers and facilitators and its uptake, if HIV-negative. The assessment will also include measures that we will develop from the focus group data to assess participants' knowledge, attitudes, and behavioral intentions toward TasP and PrEP use. Validated measures will include event-level characteristics of sexual risk episodes over the past 3 months, using the timeline follow-back interview method, with information on sexual activities, relationship with partner(s), partner gender, use of alcohol or drugs prior to or during, and use of condoms for each episode. Phase 3 will also involve fidelity monitoring of participants' use of the intervention, including information about when they check or receive messages, whether they reply to messages or input information via messages, and whether they log calls to study staff.

Study Outcomes

The primary outcome of the study will be levels of and increases in TasP or PrEP uptake in the intervention group compared with the control group, as determined by using assessment data from phase 3. Secondary outcomes include increases in levels of TasP- and PrEP-specific knowledge, favorable attitudes, and behavioral intentions regarding TasP and PrEP among participants in the intervention group. Lastly, we will explore decreases in sexual risk behaviors in the intervention group relative to the control.

Planned Analyses

For the qualitative analyses in phases 1 and 2, we will independently read and code professional transcriptions of the focus groups and interviews, and will convene regularly to discuss emerging themes and systematically establish categories. Finalized thematic codes will provide an exhaustive categorization tool of concepts and themes described by participants. Multiple coders will analyze subsets of data, interrater reliability will be assessed, and any discrepancies will be resolved with discussion.

In phase 3, we will first assess the randomization process by comparing baseline demographic variables of participants in each arm; we will incorporate any variable for which randomization did not result in equal proportions in each arm into the multivariate models as a potential confounding variable. Next, we will conduct primary inferential analyses to test our primary hypothesis (ie, that messages sent over social media will increase TasP and PrEP uptake among the men in the intervention arm versus the control arm) followed by our secondary (increases in knowledge of, more favorable attitudes toward, and behavioral intentions regarding TasP and PrEP use between men in the intervention and control arms) and exploratory (decrease in sexual risk behaviors among men in the intervention arm in comparison with the control arm) hypotheses. Since the primary and tertiary outcome measures are binary, we will first compare proportions by randomization arm separately for each measurement period using standard bivariate analytic techniques (eg, Spearman rank-order correlations, odds ratios, and Fisher exact test). We will use

ordinary least squares regression on our secondary measures of knowledge, attitudes, and behavioral intentions, which we will assess using continuous scales. We will contrast outcomes in the intervention versus comparison groups over time via generalized linear mixed models. Given the binary nature of our TasP and PrEP uptake and sexual risk measures, we will specify a logit link function for our generalized linear mixed models.

We will follow an intent-to-treat design and will include data from all enrolled participants in the analysis, regardless of level of intervention use. We will compare characteristics of participants who are lost to follow-up with those who are evaluated to assess for systematic patterns that could influence results. Following intent-to-treat principles, we will include all randomly assigned participants in the data analyses.

Effect-size estimates determined through the small RCT will be essential in the design of a larger and fully powered efficacy study that tests intervention effects on TasP and PrEP uptake and behavioral risk reduction. We are well aware of the limitations of relying exclusively on small-scale pilots to determine whether novel intervention approaches are promising, namely that sizable standard errors are associated with effect sizes due to the small sample size. However, we are primarily interested in exploring the pattern of results for any evidence of support for the intervention's influence on the primary and secondary outcomes. Our proposed sample size of 100 will be sufficient to detect an effect size of 0.3 or greater between the 2 groups, with 80% power and a 2-tailed alpha level of .05. Furthermore, we will be able to detect similar effect sizes (of ≥ 0.3) with respect to condomless anal intercourse and secondary analysis of social-cognitive behaviors.

Results

Development of this project began in May 2016. Participant recruitment for phase 1 began in August 2017 and is scheduled to be completed in August 2018. Phase 2 recruitment will begin in August 2018 and is scheduled to be completed in August 2019. Phase 3 recruitment will begin in August 2019 and is scheduled to be completed in August 2020.

Discussion

Principal Findings

The goal of this project is to add to the science about HIV prevention interventions and eHealth among black and Hispanic MSM in the United States. Successful interventions are urgently needed to reduce the burden of HIV for racial and sexual minority men. If the intervention is effective, social media messaging and culturally tailored online information could be a low-cost, high-impact way to increase uptake of HIV prevention methods in these high-risk populations. This study will also generate much-needed data on social media's utility for eHealth interventions among HIV-positive and HIV-negative black and Hispanic MSM. While eHealth has substantial potential, it remains hard to assess its ability to motivate behavioral change given the lack of data available, particularly for racial and ethnic minority MSM.

Study Limitations

There are study limitations that are important to highlight. First, given that this study will focus on HIV-positive and HIV-negative black and Hispanic MSM living in the Providence Metropolitan Area, our findings may not generalize to similar men living in other areas of the United States. Second, our results will be based on data that are self-reported by participants, which is subject to recall and social desirability biases. Third, the website and social media messages that we will develop, based on feedback from the focus groups and cognitive interviews, will be limited by the constant evolution of technology and its outpacing of research.

Study Strengths

Despite these limitations, this study has several strengths. First, it uses a combined approach to TasP and PrEP uptake that leverages advances in social media as a platform for motivating behavioral change to potentially overcome some of the noted barriers to use of HIV treatment and prevention services. Second is the use of social media messages grounded in IMB and SCT

to provide targeted groups with timely information and motivational cues to access the website about TasP and PrEP. A third advantage is that the website will be culturally tailored and specifically designed by and for HIV-positive and HIV-negative black and Hispanic MSM. Fourth, findings from this research have the potential to influence policy guidelines and recommendations for TasP and PrEP uptake for high-risk groups.

Conclusions

Development and evaluation of this newly developed website will allow for improved implementation and delivery of TasP and PrEP, and will help prevent HIV acquisition and transmission among high-risk HIV-positive and HIV-negative black and Hispanic MSM in the United States. We will use the results of this study for a larger-scale trial to test the effectiveness of the combined messages, plus the website, on behaviors leading to HIV treatment and prevention for these 2 populations. In addition, we will conduct future research to examine the long-term effects of the website on TasP and PrEP adherence among their users.

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Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention

IMB: information-motivation-behavioral skills

MSM: men who have sex with men

PrEP: preexposure prophylaxis

RCT: randomized controlled trial

SCT: social cognitive theory

TasP: treatment as prevention

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Protocol

Toward Increasing Engagement in Substance Use Data Collection: Development of the Substance Abuse Research Assistant App and Protocol for a Microrandomized Trial Using Adolescents and Emerging Adults

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Abstract

Background: Substance use is an alarming public health issue associated with significant morbidity and mortality. Adolescents and emerging adults are at particularly high risk because substance use typically initiates and peaks during this developmental period. Mobile health apps are a promising data collection and intervention delivery tool for substance-using youth as most teens and young adults own a mobile phone. However, engagement with data collection for most mobile health applications is low, and often, large fractions of users stop providing data after a week of use.

Objective: Substance Abuse Research Assistant (SARA) is a mobile application to increase or sustain engagement of substance data collection overtime. SARA provides a variety of engagement strategies to incentivize data collection: a virtual aquarium in the app grows with fish and aquatic resources; occasionally, funny or inspirational contents (eg, memes or text messages) are provided to generate positive emotions. We plan to assess the efficacy of SARA's engagement strategies over time by conducting a micro-randomized trial, where the engagement strategies will be sequentially manipulated.

Methods: We aim to recruit participants (aged 14-24 years), who report any binge drinking or marijuana use in the past month. Participants are instructed to use SARA for 1 month. During this period, participants are asked to complete one survey and two active tasks every day between 6 pm and midnight. Through the survey, we assess participants' daily mood, stress levels, loneliness, and hopefulness, while through the active tasks, we measure reaction time and spatial memory. To incentivize and support the data collection, a variety of engagement strategies are used. First, predata collection strategies include the following: (1) at 4 pm, a push notification may be issued with an inspirational message from a contemporary celebrity; or (2) at 6 pm, a push notification may be issued reminding about data collection and incentives. Second, postdata collection strategies include various rewards such as points which can be used to grow a virtual aquarium with fishes and other treasures and modest monetary rewards (up to US \$12; US \$1 for each 3-day streak); also, participants may receive funny or inspirational content as memes or gifs or visualizations of prior data. During the study, the participants will be randomized every day to receive different engagement strategies. In the primary analysis, we will assess whether issuing 4 pm push-notifications or memes or gifs, respectively, increases self-reporting on the current or the following day.

Results: The microrandomized trial started on August 21, 2017 and the trial ended on February 28, 2018. Seventy-three participants were recruited. Data analysis is currently underway.

Conclusions: To the best of our knowledge, SARA is the first mobile phone app that systematically manipulates engagement strategies in order to identify the best sequence of strategies that keep participants engaged in data collection. Once the optimal strategies to collect data are identified, future versions of SARA will use this data to provide just-in-time adaptive interventions to reduce substance use among youth.

Trial Registration: ClinicalTrials.gov NCT03255317; <https://clinicaltrials.gov/show/NCT03255317> (Archived by WebCite at <http://www.webcitation.org/70raGWV0e>)

Registered Report Identifier: RR1-10.2196/9850

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KEYWORDS

engagement; microrandomized trial; just-in-time adaptive intervention

Introduction

Substance use remains a major public health issue [1,2] due to its associations with risky behaviors (eg, intoxicated driving, violence, risky sexual behaviors, etc) and short-term (eg, injury) and long-term health consequences (eg, development of substance use disorders) [3-6]. Substance use typically begins during early adolescence (typical age, 12-17 years), with emerging adults (typical age, 18-25 years) having the highest prevalence [5]. According to the National Survey on Drug Use and Health, 11.5% of adolescents reported alcohol use and 6.1% reported binge drinking (5 or more drinks) in the past month; 59.6% of emerging adults reported drinking and 37.7% reported binge drinking in the past month [5]. Marijuana is the most commonly used illicit drug in the United States, with 7.4% of adolescents and 19.6% of emerging adults reporting its use in the past month [5]. In addition, the legalization of medical and recreational use of marijuana in several states has paralleled the decreasing perceptions of risk [7-9]. This trend is concerning because marijuana use may affect the neuro-maturational development of the brain among youth [10-12], potentially compromising decision-making and inhibitory control functioning [10-13]. Finally, prescription pain medications are the next most commonly misused substance, with 7.4% of adolescents and 2.8% of emerging adults reporting use in the past month [5]. Importantly, the risk of overdose increases when binge drinking is combined with prescription opioids and sedatives [14].

Longitudinal panel studies show that, as youth develop, evolving interactions between individual, social, and community risk and protective factors can decrease or accelerate substance use trajectories [15-18]. However, there is a critical knowledge gap about the temporal processes that underlie substance use among youth (eg, youth have greater rates of binge drinking). Knowledge about these temporal processes can enable better understanding of the real-time antecedents and sequelae of substance use and can inform the development of just-in-time adaptive interventions (JITAs) (eg, for craving, high-risk activity spaces, negative affect, and stress) [19-21]. Mobile phones provide a promising platform in this regard. Mobile phones are with us most of the time, which creates opportunities for frequent in situ data collection about the temporal processes underlying substance use. Among tech-savvy adolescents and

emerging adults, mobile phones are also pervasive; 92% of teens (age, 13-17 years) go online daily, and 73% of them have a mobile phone, which is fairly balanced across racial groups, with 85% of African Americans, 71% of Caucasians, and 71% of Hispanics having a mobile phone [22].

However, sustaining self-reported data collection is challenging in mHealth [23,24]. Self-reporting rate is generally low for mHealth data collection apps [25], and the same is true for substance use apps. A recent review of mHealth apps for substance use (including short message service [SMS] text messaging and apps) concluded that engagement is a critical limitation, with most use declining quickly over brief periods of time (2 weeks to 3 months) [26]. However, only few studies included adolescents or emerging adults [27]. The limited research on behavioral health apps among youth also found engagement challenging, potentially because youth can become habituated to apps [24] or due to competing demands from the frequent use of other apps, such as social media [22] or entertainment apps [28].

To date, there has been little work on increasing self-reporting rates of substance use data [29-31]. Sensor technologies can partially mitigate low self-reporting rates because sensors require no additional effort other than carrying the device [32,33]. However, detecting substance use by sensors is new and requires further validation. Bae et al [34] used mobile phone data to detect drinking episodes; SCRAM [35,36] and BACTrack Skyn [37] are wearable sensors that can continuously measure blood alcohol levels. However, such sensors do not exist for other substances, and important correlates of substance use such as stress level and mood cannot yet be reliably detected using sensors [38]. Therefore, self-reporting remains a valuable method to obtain substance use-related data. Previously, financial incentives were used, often along with frequent staff contact, to increase the rates of self-reporting [39-41]; however, both these strategies are prohibitively expensive for larger studies over longer periods of time. Other approaches are needed for engaging participants to self-report.

In this paper, we describe a mobile phone app, Substance Abuse Research Assistant (SARA), intended to enhance participant engagement in self-reporting. We also describe a micro-randomized trial (MRT) [42,43] design to rigorously test several *engagement strategies* we built into SARA. To our

knowledge, the SARA study will be the first [44] to examine how the effect of engagement strategies may vary with both time and context (eg, negative affect, stress, loneliness). Our vision for SARA is an “engagement first” approach, where engagement strategies are employed to increase or sustain self-reporting over extended periods of time. An important goal of SARA is to reduce staff time and financial incentives using nonfinancial engagement strategies that are grounded in behavioral science theories (such as operant conditioning [45-48] and reciprocity [49-51]). In the future, we plan to use the collected data to trigger interventions aimed at reducing substance use. This paper provides a detailed description of SARA, including the theoretical foundation of SARA’s different engagement strategies, and describes the study design we used to test the efficacy of SARA’s engagement strategies over time.

Methods

Substance Abuse Research Assistant

SARA is a mobile phone app aimed at increasing self-reporting of substance use data from adolescents and emerging adults. The app runs on both Android and iOS platforms. To collect data about correlates of substance use, every day, participants are prompted to complete a survey and 2 active tasks. SARA’s key innovation is the variety of engagement strategies it incorporates to incentivize and support this data collection. The base engagement strategy is a virtual aquarium, which starts empty, but as a participant provides more data, the fish population grows and treasures accumulate. In addition to the aquarium, other strategies such as push notifications with inspirational messages, memes, and informative visualizations

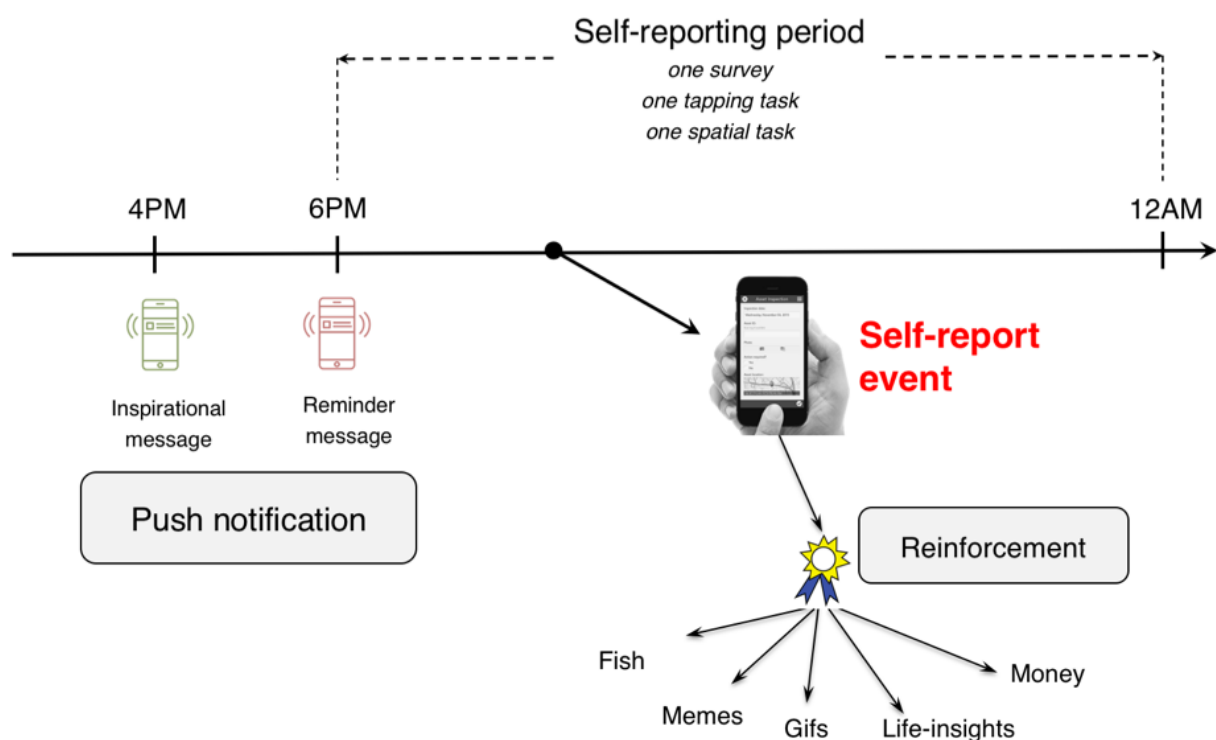
of self-report data are used to enhance engagement with self-reporting. SARA consists of 2 modules: the data collection module and the engagement module (Figure 1).

Data Collection Module

SARA’s data collection module deals with procuring self-reported data. SARA currently supports 2 types of self-reported data collection. The first is provided by active tasks. Active tasks, which were first introduced in the Apple Research Kit [52], constitute intuitive user interactions that allow researchers to *objectively* measure reaction time, spatial memory, gait, problem-solving skills, etc. SARA’s first active task serves as a measure of spatial memory, a random sequence of 5 seashells lights up in a 2-dimensional grid of 9 seashells. Participants are then asked to repeat the sequence. The second active task is a tapping task in which participants tap 2 buttons alternately for 10 seconds. The number of completed taps gives a measure of reaction time. The reason for choosing the tapping and spatial tasks is that spatial memory and reaction time may vary based on substance use-related intoxication [53,54].

The second type of data collection is a daily survey in which participants report their daily feelings and activities (ie, stress level, mood, loneliness, hopefulness, amount of free time, and excitement) [55-58]. On Sundays, an extra set of questions assesses the past week’s frequency of substance use (alcohol, cannabis, and tobacco), motives and riskiness of use (for alcohol and marijuana), impulsivity, and intentions to avoid alcohol and marijuana use in the upcoming week [8,59-63]. [Multimedia Appendix 1](#) contains the survey questions and the screenshots of the active tasks.

Figure 1. Daily timeline for engagement strategies in Substance Abuse Research Assistant (SARA). Push notifications are sent prior to data collection. Reinforcements are provided after data collection.



In the current version, participants self-report 1 survey and 2 active tasks (1 tapping task and 1 spatial task) every day between 6 pm and midnight. We selected this time window for the following reasons: (i) 6 pm to midnight provides a large enough time period to self-report, (ii) to capture a summary of most of the day using the survey in the evening, and (iii) to capture intoxication via active tasks since substances are typically used by youth in the evening [64].

Engagement Module

The engagement module of SARA contains several engagement strategies to increase self-report completion. These engagement strategies can be grouped as follows: (1) postdata collection rewards, (2) predata collection incentives, and (3) reminders to self-report. In addition, SARA contains other enhancements to support engagement, for example, occasional human support by SMS text messages or phone calls when participants temporarily disengage; a small amount of money, and an overall coherent user experience so that the app is easy to use, and the engagement strategies appear to be part of one app. Since SARA focuses on reducing financial incentives, we took several measures so that the engagement strategies are indeed effective for the target population.

First, we grounded the strategies in behavioral theories on influencing the intended action. Second, we followed a user-centered design process, where we conducted 3 focus groups (N=21, mean age 19.9 years) and a pilot study (N=17, mean age 21.2 years); a majority of the participants in these studies (67% in focus groups and 100% in the pilot study) reported binge drinking (5+ drinks at 1 occasion) or marijuana use in the past 3 months. We describe below the engagement strategies that are supported by theories and the user-centered design process.

Postdata Collection Rewards

Providing rewards after the successful completion of an intended behavior (eg, self-reporting in SARA) is a well-established method to shape future behavior [45,46]. Over the last few decades, the operant conditioning literature has extensively investigated how consequences shape behavior. According to the operant conditioning theory, the following are the 2 key ideas to influence the effectiveness of rewards: (1) Immediate contingent reward: rewards are more efficacious if they are given immediately and only after the intended behavior happens. Delaying rewards after the intended behavior or providing rewards after nonintended behaviors will make the reward less efficacious [47,48]. (2) Value of the reward: the rewards need to be valuable enough to trigger the intended behavior. One method to provide high enough value is to provide a variety of rewards; thus, even if one reward is less effective in a particular context, there is a higher likelihood that another reward can substitute for the less effective reward [65]. SARA employs these 2 ideas from operant conditioning as follows. First, ensuring immediacy and contingency was trivial; we provide the rewards immediately and only after self-reports. To ensure value, we have 2 types of rewards, (1) a growing virtual aquarium and (2) memes and life insights. We present below

their design along with supporting evidence from prior work and user-centered design to show that the strategies can indeed engender reward value.

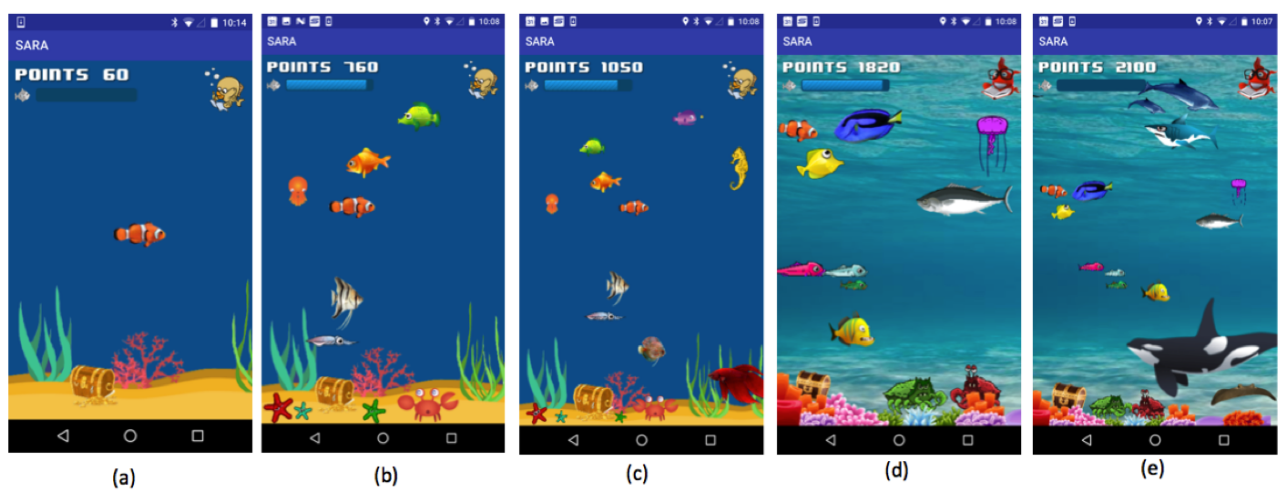
A Growing Virtual Aquarium

In SARA, a virtual aquarium environment grows richer as more self-reports are completed (Figure 2). Every time participants finish either the survey or the 2 active tasks, they earn 30 points toward the aquarium. For the longer survey on Sundays, 50 extra points are rewarded. New fish are unlocked as specific numbers of points are accumulated. Multimedia Appendix 2 lists the fish in the SARA aquarium and the corresponding numbers of points that unlock them. SARA is set up so that 1 fish can be unlocked almost every day if both the survey and active tasks are completed. Every time a fish is unlocked, a fun fact about the fish is also given; for example, when a goldfish is unlocked, participants see the message “Do you know goldfish can recognize faces?” An exception to the 1-fish-a-day rule is made for the first 2 days of the study, when SARA provides 2 fish per day. Initially, these extra fish are given to quickly condition the participant to the fact that interesting fish are unlocked if they self-report [48]. SARA makes the aquarium environment more game-like by introducing levels; after 15 days of self-reporting, participants graduate from a fishbowl environment to a sea environment. Levels help prevent cluttering as more fish are unlocked, while increasing the participants’ interest. In addition, for streaks of self-reporting, participants can earn treasures such as pearls and gemstones. Multimedia Appendix 3 lists the different pearls and gemstones available in SARA and the corresponding self-reporting streaks that can unlock them.

The growing aquarium generates reward value based on the conceptualization of engagement as a “subjective experience” [44,47,48]. The aquarium is intended to generate positive subjective experience by creating enjoyment through collection of fish in a game-like environment. Rewarding self-reporting with points or fish also intends to promote positive subjective experiences by linking self-reporting behaviors with positive emotions (eg, joy and pride). Furthermore, once participants are initially engaged, the aquarium extends the positive experience by adding complexity through the aforementioned fun fish fact, levels, and treasures. Adding such complexity makes participants feel that their efforts are being reciprocated by the designers who have invested additional effort in creating new features and challenges; this sense of reciprocation may motivate participants to engage further [66].

Finally, an aquarium representation was chosen because aquariums have been used successfully to represent rewards in wellness apps in the past—notably in Fish n’ steps [67] and BeWell [68]. A recent commercial game known as “Abyssrium,” where a user has to grow an aquarium over time, has been downloaded more than 30 million times and has received the game of the year award in 2016 [69]. Participants in the user-centered design process also found the aquarium metaphor appealing (eg, focus group participants rated the SARA aquarium 3.9 stars out of 5 for use in a research study).

Figure 2. The evolution of Substance Abuse Research Assistant (SARA)’s aquarium environment as data is collected. Panels a, b, c, d, and e respectively show the state of aquarium if a participant self-reports for 1, 7, 14, 24, and 30 days.



Memes, Gifs, and Life Insights

Although the aquarium is expected to promote engagement, it may lose its novelty over time. Therefore, SARA includes other post-data collection rewards in the form of memes or gifs and life insights. Once participants complete the daily survey part of the self-input, they may receive a meme or an animated gif. The meme or gif is intended to be either funny or inspirational. Memes and gifs are chosen because they can generate reward value by positive emotions and encouragement [44,47,48,70]. Furthermore, the nonjudgmental nature of included memes or gifs is consistent with other substance use interventions [70]. The memes and gifs in SARA were generated using Amazon’s Mechanical Turk and reviewed by undergraduate research assistants (RAs) who were of the same age as the target population. Participants in the user-centered design process for SARA also found the memes or gifs as acceptable forms of rewards (eg, on a scale of 1=strongly dislike to 5=strongly like memes or gifs as rewards for self-report, the average rating among a pilot study sample was 3.85).

In addition to memes or gifs, the participants may receive a life insight after they complete the active tasks portion of the data collection. Life insights are visualizations of self-reported data from the past. SARA’s life insights are trends of the various data collected using daily survey and active tasks over the past 7 days. SARA contains a life insight for each of the following data types: (1) daily stress, (2) amount of free time in the day, (3) degree of loneliness in the day, (4) level of fun on the day, (5) how new and exciting were the days, (6) tapping speed, and (7) seconds taken to finish the spatial task. Note that 1-5 are gathered from the daily survey and 6-7 are gathered from the active tasks (see [Multimedia Appendix 4](#)). Life insights can generate reward value because individuals strive to understand themselves and gain self-relevant knowledge [71-73]. People are frequently unclear about their personal abilities and they learn about themselves by attending to and seeking self-relevant information [71,72,74,75]. Consistent with this notion, previous work has demonstrated that people are interested in receiving feedback about their past self-reported experiences [76]; in fact, most health apps and wearables (eg, fitbit) use visualizations of past data to provide feedback to their users. Participants in

the user-centered design process for SARA were also quite interested in seeing their data on life insights (eg, on a scale of 1=strongly dislike to 5=strongly like life insights as rewards for self-report, the average rating among a pilot study sample was 3.92).

Predata Collection Incentive

Sociopsychological perspectives [49-51] suggest that reciprocity, that is, returning a favor, is an innate human tendency. Drawing on these perspectives, SARA sometimes provides incentives before (ie, not conditional on) self-reporting to facilitate participant reciprocity via subsequent self-reporting. SARA may issue a youth-focused inspirational message as a push notification at 4 pm, 2 hour before the data collection period starts. We selected 4 pm because adolescents or emerging adults are likely to be out of school at that time and hence are likely to notice the notification. This time is also close enough to data collection time (6 pm) so that providing an incentive may facilitate participant reciprocity via survey or active task completion. To facilitate participant reciprocity, we provide inspirational messages. From the user-centered design process, we found inspirational quotes in the form of song lyrics and celebrity quotes, which might be appealing to youth. Please refer to [Multimedia Appendix 5](#) for the list of quotes used in SARA. Once again, this repository of messages was assembled and filtered by the undergraduate RAs who were of the same age as our target population. In the pilot study, we asked participants how much they liked the inspirational quotes as an incentive for self-report (1=strongly dislike, 5=strongly like); the average rating was 3.3.

Reminder Notifications

Past research has demonstrated that reminders can increase engagement [44]. SARA thus provides a message at 6 pm to remind participants to report data. The reminder message is sometimes appended with additional content, such as “you are close to unlocking a new fish,” “you are close to finishing a streak and earning some money,” or “it only takes a minute to collect data in SARA.” The additional content tries to increase adherence by altering the perception of the value of self-reporting by reminding the participants of rewards that follow or that self-reporting does not require a lot of effort [77].

We selected 6 pm to send the reminder notification because it was the start time for the daily 6 pm to midnight self-reporting period discussed previously.

Other Enhancements to Support Engagement

SARA includes a few additional enhancements to support the abovementioned engagement strategies:

Financial Incentives and Human Support

One potential issue with the aquarium, memes, and life insights is that they are new rewards and participants may need time to perceive their full value. For example, unlocking fish and growing a virtual aquarium will be new to participants at the start of the study and they need to receive rewards several times before understanding what to expect. Therefore, participants may need additional sources of reinforcement that are rewarding right from the start [65]. Earlier work has demonstrated the utility of financial incentives [39,40] and human support [41] in promoting engagement. Participants in the user-centered design process for SARA also were very interested in financial incentives (eg, 95% of focus group participants reported that money bonuses would very much increase self-reporting in SARA). Hence, SARA includes relatively minimal financial incentives and human support to supplement its core engagement strategies; for every 3-day streak of self-reporting, that is, completing the survey and active tasks each day, participants can earn 1 dollar. For completing the longer weekly survey on Sunday, an extra 50 cents can be earned. For a 90% self-report completion rate, most participants can earn US \$12 or less in a 30-day study (US \$13 if self-report completion rate is 100%). Note that this is a fraction of what daily substance use studies normally pay for self-reporting (eg, US \$1-4 dollars per day) [21,78].

In addition, if participants do not self-report, they receive SMS text messages from a study phone number. The first SMS text message is sent after 2 days of no self-reporting. If participants still do not self-report, a SMS text message is sent after 3 additional days of no self-reporting. The SMS text message follows a prespecified template (see [Multimedia Appendix 6](#)), which can be automated in future versions of SARA. After 7 days of no self-reporting, participants receive a phone call from a study team member. SMS text messaging and phone calls stop if participants neither respond nor self-report for 3 weeks.

User Experience

In SARA, we maintain a coherent user experience using an aquarium theme throughout the app. For example, in the spatial task, we use seashells to match the aquarium theme instead of flowers originally used by the Apple Research Kit [52,79]; after data collection, rather than only providing memes or life insights, we use animations consistent with the aquarium theme; divers swim into the aquarium and inform the participants that they earned a reward (eg, meme or life insight). Further attention-to-detail is provided to improve user experience; for example, Sunday's survey contains 2 parts where participants answer a few questions about their day, followed by a few questions about the past week. Since Sunday's survey is longer than other days, we include a fun question right after the daily

questions to entertain and energize participants before asking them additional questions about the past week. This fun question is randomly selected from a set of 5 questions in [Multimedia Appendix 7](#).

With this, we conclude the description of different engagement strategies in SARA. [Figure 3](#) provides a summary of the engagement strategies and how these strategies affect various theoretical constructs to influence self-report completion in SARA.

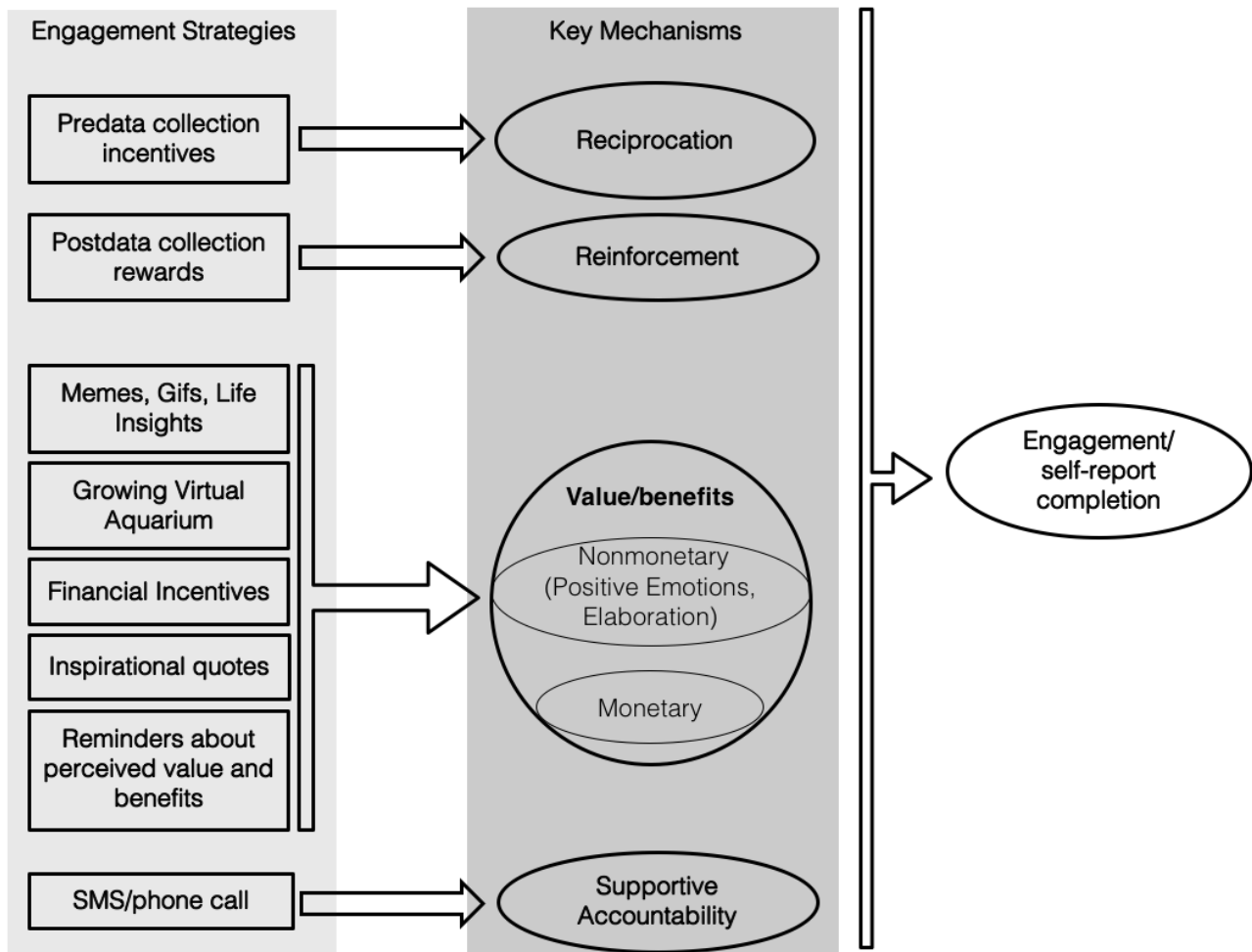
Implementation Details

We used the cross-platform JavaScript framework Ionic to build the Android and iPhone versions of SARA. The aquarium part uses the Phaser 2D game library for the animations. All the self-reported data in SARA are encrypted to comply with the Health Insurance Portability and Accountability Act (HIPAA). All data are stored in Amazon S3, a HIPAA-compliant data storage service, and the communication between Amazon S3 and the mobile phone app is encrypted with RSA 2048 and AES-256 [80].

Objective

In the previous section, we described several of SARA's novel engagement strategies. Although SARA engagement strategies were designed to influence self-report completion among youth who use substances, the effectiveness of these strategies is unknown. Important questions include whether different SARA engagement strategies lead to higher self-report completion and how their effectiveness is moderated by context (eg, negative affect, stress, loneliness, etc). Ineffective engagement strategies may aggravate participants, and participants may habituate even to an initially effective engagement strategy [81,82], resulting in a decrease, over time, in the effectiveness of the strategy. Similar drawbacks might occur if an engagement strategy is used in a context in which it is ineffective; indeed, the current context of each participant may influence the effectiveness of an engagement strategy [77]. One way to gain insight into these questions is by experimentally manipulating the engagement strategies over time. In other words, the manipulation can inform the development of a policy for adaptive engagement strategy delivery to keep participants engaged in self-reporting. Recently, MRTs have been proposed as a method to develop JITAIs for mHealth [42,43]. In SARA, the intervention is composed of the engagement strategies, such as giving a meme or issuing an inspirational message. In MRTs, study participants are randomized sequentially, often multiple times a day, to receive different intervention components. Several key elements in MRTs are decision points and proximal outcomes. *Decision points* refer to the time points when participants are randomized. In SARA, there is a 4 pm decision point at which a participant is randomized to receive an inspirational message via push notification or receive nothing. Once a participant is randomized at a decision point, the *outcome* of using an engagement strategy can be measured *proximally*. A proximal measure for the 4 pm inspirational message is whether or not the participant self-reports later on the same day. For more details on MRTs, we refer the readers to [42,43,83]. In the following, we describe the MRT protocol for SARA.

Figure 3. A conceptual diagram of how the different engagement strategies should affect self-report completion.



Study Protocol

We plan to run a 30-day MRT. Prior to the study, potential participants are screened, and eligible participants complete an in-person intake session with a study recruiter. Within the 30-day study, each participant is randomized at each of 4 decision points per day. After the 30 days, each participant takes part in a follow-up phone interview and provides feedback on using SARA for a month. The details of the study are as follows:

Study Setting and Eligibility

The 30-day MRT is conducted at the University of Michigan. Study participants are recruited from the University of Michigan Hospital Pediatric and Adult Emergency Departments. The study is approved by the Institutional Review Board of the University of Michigan Health System (HUM00121553) and is registered at ClinicalTrials.gov (NCT03255317). Patients are eligible for screening if they are aged between 14 and 24 years, understand English, are medically stable, are able to provide informed consent or assent (eg, not cognitively impaired or intoxicated), and are accompanied by a parent or guardian (for patients aged between 14 and 17 years). Individuals are eligible if they 1) have an Android or an iPhone mobile phone on which the app can be downloaded and 2) screen positive for past-month binge drinking (≥ 4 drinks for females and ≥ 5 drinks for males, on at least 1 occasion) or past-month cannabis use without a medical marijuana card.

Baseline Procedure

At the University of Michigan Emergency Department, recruiters monitor incoming admissions and identify patients in the target age range who do not meet the screening exclusion criteria (eg, presentation for sexual assault, droplet precautions, active vomiting, roomed in critical care). After completing an online consent or assent, participants self-administer a screening survey on a tablet, which contains questions regarding their demographics [84,85], health behaviors such as alcohol and marijuana use [8] and sleep habits [86], cell phone capabilities, and social media use. The screening survey takes approximately 8 min to complete, and participants receive a small gift valued at US \$1.00 (eg, headphones, water bottle, mobile phone armband) for completing it. Those who report past-month binge drinking or marijuana use and have access to their mobile phone while in the Emergency Department provide written consent or assent and self-administer an approximately 20-min baseline survey with items about (1) substance use frequency, consequences, overdose, and driving under the influence [86-88]; (2) violence involvement, injury, and risky sex behaviors [6,89-92]; (3) coping and mindfulness [93,94]; (4) social influences [95-97]; and (5) motivation or self-efficacy to reduce their alcohol and marijuana use [98,99].

Then, the recruiters collect contact information from the participants. Recruiters ensure that participants install SARA on their phone during the intake since in the pilot study prior

to this trial, we have found that many potential participants did not install the app after they left the intake session. Basic instructions on how to use the app are provided during intake, followed by motivational statements regarding participant's stated barriers to using SARA regularly. Participants receive US \$20 cash for completing their intake visit.

The 30-Day Microrandomized Trial

Following the intake session, participants start the 30-day MRT with SARA. Each day, participants are requested to complete 1 survey and 2 active tasks between 6 pm and midnight. Participants are randomized at the following 4 decision points each day:

1. *4 pm reciprocity notification*: Every day at 4 pm, with a probability of .5, participants are randomized to either receive a push notification with an inspirational message—a song lyric or a quote from a contemporary celebrity—or to not receive anything.
2. *6 pm push reminder notification*: Every day at 6 pm, a reminder notification is issued. The notification may be one of the following 2 types, randomized at .5 probability:
 - a. A simple reminder to complete a survey and 2 active tasks
 - b. A reminder to complete a survey and 2 active tasks, along with an additional persuasive message. The additional persuasive message may be one of the following 3 messages:
 - “Do you know it only takes a minute to fill out the survey and active tasks?”
 - “Do you know you can earn money if you complete a 3-day streak?”
 - “You are close to unlocking the next fish for the aquarium.”
3. *Reinforcement after survey completion*: If the survey is completed, participants are randomized at .5 probability to receive or not receive either a meme or a gif as a positive reinforcement. If a reinforcement is delivered, there is a .5 probability to receive a meme and a .5 probability to receive a gif.
4. *Reinforcement after active task completion*: If active tasks are completed, participants are randomized at .5 probability to receive or not receive a life insight as a positive reinforcement.

Note that not all the engagement strategies in SARA are randomized. The randomizations in 1-4 mentioned above are motivated by scientific questions concerning the abovementioned engagement strategies in SARA. Specifically, we randomize the push notifications because they can interrupt the participant and are intrusive, thus potentially reducing engagement. The other engagement strategies are not push notifications, so there is low risk of interruption; for example, the participant decides whether to open the app, complete self-reports, and receive the rewards. We randomize the memes and life insights because of the scientific question of how funny and informative contents respectively can influence self-report completion over time [44].

Exit Procedure

Participants are contacted by telephone to complete a 1-month follow-up interview, which includes the identical measures as the screen or baseline or daily survey or Sunday's survey, as well as the following 2 new threads of questions: (1) a 30-day Timeline Followback calendar, which captures past-month alcohol and marijuana consumption [100] and (2) Likert-type and open-ended questions to capture user experience of SARA [101]. For completing the follow-up interview, participants receive a US \$30 electronic gift card of their choice (eg, Amazon, Starbucks, etc).

Analysis Plan

In this section, we describe the analysis plan to evaluate SARA. A more detailed version of the analysis plan can be found in a Center for Open Science document [102] (submitted on October 23, 2017).

Outcome Measures

The proximal outcomes of the randomizations are whether participants completed the survey and active tasks. For the inspirational message notifications at 4 pm and the reminder notifications at 6 pm, the proximal outcome is whether the survey or the active tasks are completed in the evening on the same day. For the 2 reinforcement interventions, the proximal outcome is whether the survey or the active tasks, respectively, are completed on the following day. Note that our engagement strategies are primarily designed to encourage self-reporting on the same or next day. Although the strategies may have longer term effects as well [81,82], we are interested in their effects on the same day or the next day; if these effects are consistently higher, then longer term adherence will be higher too. In addition, poststudy open-ended feedback from the participants will be analyzed to refine future versions of SARA.

Primary and Secondary Analyses

Our primary analyses will concern the following 2 hypotheses:

1. Providing the 4 pm reciprocity notification will yield a higher rate of full completion of the survey or active task on the same day than providing no intervention ($P < .025$).
2. Among individuals who complete the survey, providing a postsurvey-completion meme or gif will yield a higher rate of completion of the survey or active task on the next day than not providing meme or gif reinforcement after survey completion ($P < .025$).

We selected these hypotheses as primary since our team found these hypotheses to be the most interesting scientifically. The 4 pm randomization is designed to address the question of whether a notification intended to facilitate reciprocation (by providing an inspirational message before self-report time) is useful, and the randomization of participants upon survey completion is designed to investigate whether providing a postdata collection reward increases data collection. Furthermore, we conjecture that these hypotheses have the greatest potential to be supported. In particular, as the 4 pm notification is proximal in time to the data collection (2 hours prior), there are fewer extraneous distracting circumstances that can occur during this short time window that would reduce the

intervention effect. Both hypotheses also consider a contrast between an active agent (ie, the 4 pm notification or the meme) versus nothing. Since these 2 hypotheses are primary, we divide the standard *P* value of .05 by 2.

Our secondary analyses will concern the following 2 hypotheses:

1. The 6 pm reminder notification with an extra persuasive message will yield a higher rate of full completion of the survey or the active task on the same day than not providing the extra persuasive message.
2. Among individuals who complete the active tasks, offering a postactive task-completion life insight will yield a higher rate of the full completion of the survey or active task on the next day than not offering a life insight after active task completion.

We consider the first hypothesis as secondary because the randomization for the 6 pm reminder is between 2 active agents (reminder with vs without a persuasive message). This implies that the additional effect of the persuasive messages may be small; thus, this hypothesis has a more exploratory nature. We consider the second hypothesis as secondary because data must accumulate before the visualizations in life insights become interesting. In addition, this hypothesis has a more exploratory nature because our life insights are only visualizations of past data; in the future, we aim for potentially more potent life insights using prediction tools [103,104].

For both primary and secondary analyses, we will control for the following 3 covariates to reduce variance in the outcome of self-input completion: (1) whether the survey or the active tasks were fully completed on the previous day, (2) whether SMS text messages or phone calls were made in the last 24 hours, and (3) whether the app was opened in the prior 72 hours outside when a survey or active task was completed. We will not include other baseline variables such as gender and age as covariates in the primary analyses because inclusion of a covariate uses up degrees of freedom. We also anticipate that the *within-person* covariate “whether the survey or active tasks were fully completed on the previous day” will capture some of the variance due to baseline gender or age. We will also not include time as a covariate in the primary analyses for the abovementioned reasons as well. Note that the statistical methods [83] will adjust the standard errors of the estimated effects to account for within-person correlation across time in the outcome. For more details about our primary analysis plan, please refer to the Center for Open Science document [102].

Exploratory Analyses

We plan to run exploratory analyses to examine how the effectiveness of engagement strategies changes over time (we conjecture that the effectiveness will decrease). We will also run additional exploratory analyses to assess effect moderation. We will examine how the effect of engagement strategies is moderated by gender, weekdays versus weekends, and whether the day is Sunday versus other days of the week (we expect that the completion rate for the longer Sunday’s surveys may be lower than that for other days). We initially planned to assess age and phone type (Android or iPhone) as moderators; however, we did not include these variables because recruitment

thus far indicates that very few participants in the study have Android phones or are below the age of 18 years.

Sample Size

We started recruiting for the study on August 21, 2017. Recruitment concluded on February 28, 2018. We recruited 73 participants for the study.

Statistical Analyses

In mHealth, it is common to collect time-varying measures of the participants’ context (such as stress, mood, and loneliness from the self-report assessments). The provision of engagement strategies is time-varying as well; that is, at each decision point, participants can receive different options of the engagement strategy. A key statistical issue is that covariates (measures of the participant’s context) at a time point can be affected by past engagement strategies. For such a setting, Boruvka et al [83] proposed a method to estimate the causal effects of interventions on continuous outcomes. However, in SARA, we are dealing with a binary outcome (whether participants self-reported or not). Multimedia Appendix 8 contains details of a method that we have developed, which extends the work of Boruvka et al to binary outcomes. We will use RStudio 1.1.453 to run the statistical analysis.

The open-ended qualitative data from exit interviews will be coded using thematic analysis [105]. The qualitative analysis will be performed using NVivo 11.

Missing Data

Since our outcome is adherence to self-report completion, not completing self-reports is not missing data for our study. However, missingness can happen in the study if participants uninstall the app in the middle of the study. To account for such missingness, we will conduct the following 3 versions of the primary analysis: (1) only include participants who had the app installed for 30 days, (2) include all participants and include only days when the app was installed, and (3) include all participants and data for both installed and uninstalled days; for the uninstalled days, the 4 pm and 6 pm notifications will be imputed, and the outcome will be considered as “self-report noncompletion.” More details on how missingness will be accommodated can be found in the Center of Open Science document [102].

Results

We started recruiting for the study on August 21, 2017. Recruitment concluded on February 28, 2018. We recruited 73 participants for the study. Data analysis is currently underway.

Discussion

Future Work

To the best of our knowledge, this study is the first MRT to systematically explore the efficacy of different engagement strategies on increasing self-reporting of substance use data among adolescents and emerging adults. The results of this trial will answer how different engagement strategies affect self-reporting and to what degree (ie, effect size). We will also

learn whether the effectiveness of the strategies varies over time. The qualitative data from the exit interviews will help us to further triangulate and understand the findings of the quantitative analysis. Moreover, the exit interviews' open-ended feedback about the app will help us further fine-tune the app.

For future studies, the analysis of the collected data can be used to initialize machine learning algorithms with the goal of providing engagement strategies in contexts (eg, stress level, loneliness, location, and weekend or weekdays), and at times, they are most effective. In particular, we will use the resulting data to train an initial policy for reinforcement learning algorithms such as "contextual bandits" [106]. As data accumulate on a participant, these algorithms increase the chance of providing the engagement strategy option that is most effective in a particular context and decrease the chance of providing an engagement strategy option that is less effective [107].

Another important direction of future work is the development of therapeutic interventions to prevent substance misuse. The daily surveys and active tasks will provide both subjective and objective data on substance use and related factors (eg, mood) over time. The Sunday's survey will uncover the days when substance use events happened; we will use these data as labels and the daily survey (ie, stress, emotion, or loneliness) or active tasks (ie, spatial memory, reaction time) as features to create machine learning models of impending substance use events. Therapeutic interventions will be provided, with high probability, at the time of impending substance use (or when participants are likely to engage in intervention content). Future versions of SARA will integrate these JITAIs to reduce substance misuse. Note that data-driven JITAIs to reduce substance use require maintenance of sufficient engagement of self-input completion.

Finally, one more future direction is to include sensor data collection from phones and wearables. Sensor data can be useful in multiple ways for SARA, such as (1) reducing self-input burden with predictions, for example, loneliness can be measured by inferring social interactions from the phone [33]; reducing self-input burden may increase engagement [77] and (2) risky times of substance misuse can be preanticipated from sensors; we expect that substance use events co-occur with certain behavioral markers that can be captured using sensors, for example, when participants are close to liquor stores or texted friends with whom they previously engaged in substance misuse [34].

Limitations

Few limitations of this study are as follows: first, this study is not designed to confirm that the SARA is more effective than other apps in collecting substance use-associated data. This trial is only designed to optimize the further development of SARA. We believe that this is a necessary first step since the science of engagement in mHealth is currently in its infancy. This MRT will inform the selection and adaptation of engagement strategies, as well as the development of future versions of SARA, which can be used as an experimental arm in randomized trials.

Second, the current version of SARA is limited because the design primarily focused on increasing willingness, that is, to the extent a participant is motivated to engage in self-reporting. Prior literature suggests 2 other methods to influence engagement [44,77,108-111]: (1) need, namely an individual's recognition that there is a discrepancy between his or her present state and a preferred future state, and (2) ability, namely the extent to which the individual has the knowledge, experience, skills, and capacity to engage in data collection. Although SARA is not currently designed to experiment with ability or need, SARA may influence them indirectly; for example, the reminder prompts before data collection can address forgetfulness and enhances the ability of participants to collect data. Furthermore, SARA sets clear goals, monitors engagement with aquarium progression, and offers timely feedback [112]. Thus, if participants become engaged with the aquarium or other incentives, they may recognize the need to engage.

A third limitation is the limited funding of the SARA mobile app, which is novel and exploratory in nature. Limited funding constrained our sample size. We also could not implement several features that were requested during user-centered design process; for example, better aesthetics of the fish, interactivity such as touching and interacting with fish, or personalization of such customizable background of the aquarium. In the future, we will use the results of this pilot study and apply for grants that can support larger studies and more resources for app development.

Finally, the study lacks therapeutic interventions to improve substance use outcomes. However, the engagement-only approach provides naturalistic data on substance use and related factors at the daily level, allowing us to study in-the-moment precedents and sequelae of substance use among adolescents and young adults. A better understanding of the in-the-moment precedents and sequelae of substance use is necessary to shape future therapeutic interventions that can be integrated into SARA.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Survey questions and active tasks

[[PDF File \(Adobe PDF File\), 265KB - resprot_v7i7e166_app1.pdf](#)]

Multimedia Appendix 2

Fishes and points

[[PDF File \(Adobe PDF File\), 548KB - resprot_v7i7e166_app2.pdf](#)]

Multimedia Appendix 3

Gems and pearls

[[PDF File \(Adobe PDF File\), 208KB - resprot_v7i7e166_app3.pdf](#)]

Multimedia Appendix 4

Screenshots of life-insights

[[PDF File \(Adobe PDF File\), 156KB - resprot_v7i7e166_app4.pdf](#)]

Multimedia Appendix 5

Inspirational quotes.

[[PDF File \(Adobe PDF File\), 32KB - resprot_v7i7e166_app5.pdf](#)]

Multimedia Appendix 6

Protocol for texting and phone calls.

[[PDF File \(Adobe PDF File\), 59KB - resprot_v7i7e166_app6.pdf](#)]

Multimedia Appendix 7

Fun questions in the weekly survey

[[PDF File \(Adobe PDF File\), 16KB - resprot_v7i7e166_app7.pdf](#)]

Multimedia Appendix 8

Analysis steps to assess causal effects

[[PDF File \(Adobe PDF File\), 74KB - resprot_v7i7e166_app8.pdf](#)]

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Abbreviations

- EMA:** ecological momentary assessment
- HIPAA:** Health Insurance Portability and Accountability Act
- JITAI:** just-in-time adaptive interventions
- MACQ:** Marijuana Consequences Questionnaire
- MRT:** microrandomized trial
- RAs:** research assistants
- SARA:** Substance Abuse Research Assistant

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Protocol

Characteristics of Cognitive Behavioral Therapy for Older Adults Living in Residential Care: Protocol for a Systematic Review

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Abstract

Background: The prevalence rates of depressive and anxiety disorders are high in residential aged care settings. Older adults in such settings might be prone to these disorders because of losses associated with transitioning to residential care, uncertainty about the future, as well as a decline in personal autonomy, health, and cognition. Cognitive behavioral therapy (CBT) is efficacious in treating late-life depression and anxiety. However, there remains a dearth of studies examining CBT in residential settings compared with community settings. Typically, older adults living in residential settings have higher care needs than those living in the community. To date, no systematic reviews have been conducted on the content and the delivery characteristics of CBT for older adults living in residential aged care settings.

Objective: The objective of this paper is to describe the systematic review protocol on the characteristics of CBT for depression and/or anxiety for older adults living in residential aged care settings.

Methods: This protocol was developed in compliance with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). Studies that fulfill the inclusion criteria will be identified by systematically searching relevant electronic databases, reference lists, and citation indexes. In addition, the PRISMA flowchart will be used to record the selection process. A pilot-tested data collection form will be used to extract and record data from the included studies. Two reviewers will be involved in screening the titles and abstracts of retrieved records, screening the full text of potentially relevant reports, and extracting data. Then, the delivery and content characteristics of different CBT programs of the included studies, where available, will be summarized in a table. Furthermore, the Downs and Black checklist will be used to assess the methodological quality of the included studies.

Results: Systematic searches will commence in May 2018, and data extraction is expected to commence in July 2018. Data analyses and writing will happen in October 2018.

Conclusions: In this section, the limitations of the systematic review will be outlined. Clinical implications for treating late-life depression and/or anxiety, and implications for residential care facilities will be discussed.

Trial Registration: PROSPERO 42017080113; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=80113 (Archived by WebCite at <http://www.webcitation.org/70dV4Qf54>)

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KEYWORDS

cognitive behavioural therapy; older adults; residential care; delivery; characteristics; systematic review

Introduction

Older adults living in residential care settings have a high prevalence rate of depression and anxiety disorders. A systematic review of studies involving aged care residents from North America, Europe, Middle East, Australia, New Zealand, Africa, and Asia [1] reported that the prevalence of a major depressive disorder ranged from 4.8% (13/270) to 23.5% (12/51), whereas the prevalence of depressive symptoms ranged from 14% (99/708) to 81.8% (113/138). Another systematic review that examined the prevalence of anxiety in older adults living in residential aged care [2] found that the prevalence of anxiety disorders ranged from 3.2% (31/966) to 20% (20/100), whereas the prevalence of clinically significant anxiety symptoms ranged from 6.5% (3/46) to 58.4% (118/202). The most common anxiety disorders among aged care residents were generalized anxiety disorder and specific phobias.

The high prevalence of depression and anxiety in residential care settings may be attributed to several factors, including losses (eg, social connections and personal possessions) and changes (eg, lifestyle and health) involved in transitioning to living in a residential care facility [1,3,4]. Other factors associated with depression and anxiety in older adults living in residential care include multiple chronic health problems, chronic pain, functional impairment in basic activities of daily living (eg, bathing), functional impairment in instrumental activities (eg, managing finances), sensory impairments (eg, vision and hearing), cognitive decline, loneliness, negative life events, lack of social support, perceived inadequacy of care, perceived inability to master and control external environment, a low sense of purpose in life, and low perceived autonomy [5-7]. Another contributing factor could be the patterns of interactions between nursing staff and residents of care facilities. Baltes et al [8,9] reported that residents developed learned dependency when the social environment provided consistent and immediate support for dependent self-care behaviors (eg, residents who did not attempt to eat by themselves would likely receive immediate help from staff members, whereas those who attempted to eat independently would not receive praise, encouragement, or attention). Thus, learned dependency could have a negative impact on residents' self-image and sense of control; subsequently, this could affect their psychological well-being.

To date, several approaches (eg, psychotherapy, pharmacological interventions, and music therapy) have been used to treat late-life depression and anxiety [10]. The efficacy of

psychotherapeutic interventions, particularly cognitive behavioral therapies (CBT), has been demonstrated in several systematic reviews and meta-analyses conducted in the community and residential settings. CBT represents an approach that focuses on identifying and improving maladaptive behavioral and thinking patterns to assist clients in achieving goals. CBT includes a wide range of cognitive and behavioral techniques and is structured and goal-oriented.

Focusing on community-dwelling older adults, Wilson et al [11] reported that the efficacy of CBT in treating late-life depression was equivalent to or better than that of active control interventions (eg, visual imagery and education). Similarly, summarizing findings across community-based samples, Hendriks et al [12] reported that CBT was markedly more effective than waiting list and active control conditions (eg, usual care and supportive psychotherapy) in reducing anxiety symptoms in older adults diagnosed with anxiety disorders. In addition, a more recent meta-analysis [13] reported that CBT was markedly more effective in reducing anxiety symptoms in community-dwelling older adults compared with treatment as usual or being on a waiting list.

In a meta-analysis of the outcomes of psychotherapy for aged care residents, Cody and Drysdale [14] reported that psychotherapies were effective in reducing the symptoms of depression. In addition, they found that the effect of psychotherapies was comparable to that reported in pharmacotherapy trials with depressed older adults. Despite a lack of systematic reviews specifically examining CBT in residential care settings, studies such as those conducted by Anderson et al [15] and by Blair and Bird [16] found that CBT was effective and feasible for reducing depressive symptoms in older adults living in residential care.

Given the presence of multiple medical comorbidities and functional and cognitive decline, older adults in residential care might have different needs, clinical presentations, and perceptions of and responses to psychotherapies compared with community-dwelling older adults. In addition, the complexity of presentations might entail unique implementation models requiring interdisciplinary teamwork, sustainability of the intervention, flexibility of the environment, and support of the organization [17]. Specific programs, such as the Group, Individual, and Staff Therapy (GIST) [18] and the Behavioral Activities Intervention (BE-ACTIV) [19], have been developed for residential care settings. Nevertheless, no systematic review has been conducted on techniques and delivery characteristics of CBT when employed in residential care facilities. Such a

systematic review is essential because it provides crucial information for the development of future CBT-based programs for residents in aged care. As highlighted by Kishita and Laidlaw [20] and Blair and Bird [16], identifying components of CBT programs that are specific to this population (eg, logistical issues such as how to approach residents, group size, timing, and duration of sessions) could help enhance treatment accessibility, acceptability, and outcomes. Moreover, by identifying the content of such protocols, that is, the strategies and techniques used to assist residents, clinicians may be better prepared to address the concerns of older adults living in residential aged care settings.

Methods

Objectives

This systematic review aims to describe the delivery and content characteristics of CBT for depression and anxiety for older adults living in residential aged care settings. This review adopts a broad definition of “older adults,” those aged ≥ 55 years.

Protocol and Registration

This protocol was developed to comply with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [21]. This systematic review will follow the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22]. The review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD 42017080113).

Eligibility Criteria for the Review

Participants

In this review, those studies will be included, in which (1) participants were, at least, 55 years old, (2) were living in residential care (see definition below), and (3) standardized, valid measures (self-report questionnaire, observer rating, or clinical interview) were used to record the diagnosis and severity of depressive or anxiety disorders and symptom ratings of depression or anxiety. Samples of participants might include those living with dementia or mild cognitive impairment. Furthermore, studies that recruited participants aged < 55 years but reported separate results for participants aged ≥ 55 years will be included.

Intervention

The target intervention is CBT for depressive symptoms, depressive disorders, anxiety symptoms, or anxiety disorders. Consistent with other studies [12,14], the types of psychotherapies considered to be CBT include behavioral therapy (including behavioral activation and exposure-based interventions), cognitive therapy, CBT, problem-solving therapy, rational emotive behavioral therapy, and mindfulness- and acceptance-based cognitive and behavioral therapies. Of note, studies that focused only on non-CBT interventions (eg, psychodynamic therapies, interpersonal therapies, and systemic therapies) or on psychological problems other than depression and anxiety will be excluded from this review. Moreover, studies

will be excluded if their primary aim was to reduce disruptive behaviors associated with dementia or enhance memory.

Outcomes

The primary interest of this review is the delivery and content characteristics of CBT for residential aged care settings. Delivery characteristics refer to the (1) frequency, (2) duration, and (3) mode (group vs individual) of treatment, as well as to (4) whether others were involved in the delivery of treatment (eg, nurses, other facility staff members, and family members), and (5) whether treatment was delivered alone or in combination with other interventions. In contrast, the content characteristics refer to the therapeutic techniques used (eg, behavioral activation and cognitive restructuring). In addition, information on stakeholders' reactions to these interventions will be described; such outcomes (whether assessed by a clinician, self-report, or an informant such as a staff member) will include participants' satisfaction with the CBT intervention, staff members' appraisal of the program, uptake rate, and attrition rate. Furthermore, these outcomes must be assessed with standardized, valid measures.

Setting

In this review, we will include studies conducted in residential care facilities and exclude those conducted only with community-dwelling older adults. Settings that are considered residential care facilities comprise nursing homes, aged care homes, residential aged care, and other communal living arrangements for older adults, where staff are employed to assist the residents with activities of daily living. Of note, studies conducted in retirement villages or retirement homes or hostels, where staff are only employed as on-site managers but do not provide care will be excluded.

Types of Studies

We will include empirical, quantitative studies that fulfill the criteria mentioned above. These studies could be randomized or quasi-randomized controlled trials, clinical controlled trials, cluster-randomized trials, cross-over trials, or case studies. However, commentaries and theoretical papers that describe protocols that have not been applied in residential aged care settings will be excluded.

Report Characteristics

We will include full-text papers written in English with no restrictions on the geographical location or year of publication.

Search Methods for Identifying Studies

We will be conducting a systematic search of the following databases to identify published studies: the Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL) and the specialized registers of the Common Mental Disorders Group and the Dementia and Cognitive Improvement Group), Medical Literature Analysis and Retrieval System Online (MEDLINE), EMBASE, PubMed, PsycINFO, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Abstracts in Social Gerontology (EBSCO), AgeLine (EBSCO), Social Services Abstracts (ProQuest), Sociological Abstracts (ProQuest), the World Health Organization's trials portal (ICTRP), and ClinicalTrials.gov. Next, unpublished

studies will be identified by searching the ProQuest Dissertations and Theses database, Open Access Theses and Dissertations, and Open Grey. In addition, reference lists of all included studies will be examined and a citation search on the Web of Science will be conducted to identify relevant studies that might have been missed in the database searches. Furthermore, we will correspond with the authors of these studies, if it is feasible to do so, when more information on particular studies is required.

The search terms are arrived at by adapting those used by Cody and Drysdale [14] and Hendriks et al [12]. A sample search strategy for database searching will be as follows:

("depress*" OR "dysthym*" OR "adjustment" OR "mood" OR "affective" OR "anxiety" OR "anxious" OR "worry" OR "phobi*" OR "panic" OR "obsess*" OR "compulsi*" OR "posttraumatic" OR "PTSD" OR "OCD") AND

("cognitive therapy*" OR "behavi* therapy*" OR "cognitive behavi* therapy*" OR "mindfulness-based therapy*" OR "acceptance commitment therapy*" OR "acceptance-based therapy*" OR "relaxation training" OR "activity scheduling" OR "cognitive restructuring") AND

("long-term care" OR "residential aged care" OR "aged care" OR "nursing home*" OR "assisted living" OR "care facility*" OR "residential home*" OR "care home*" OR "residential care")

Data Collection and Analysis

Selection of Studies

In this review, two reviewers will be involved in the process of selecting studies to ensure that the judgments are reproducible [23]. They will independently examine titles and abstracts of the records retrieved from the database search to remove obvious irrelevant reports. Then, the reviewers will screen the full text of the potentially relevant studies to assess their eligibility for inclusion. While one reviewer will screen all the records and papers, the second reviewer will screen, at least, 25% of them. Discrepancies between the reviewers will be resolved by discussion and consensus, and if necessary, by arbitration of a third reviewer. All initial levels of the agreement will be reported. In addition, the PRISMA flow diagram will be used to record the process of selection, as well as the numbers of records, full-text papers, and studies resulted from each stage.

Data Extraction and Management

We will use a pilot-tested data collection form to extract and record data from the included studies. The data extracted will comprise the following: publication information (eg, authors, title, journal, publication type, and geographical location wherein the study was conducted); study design (eg, randomized or quasi-randomized controlled trial, clinical controlled trial, cluster-randomized trial, cross-over trial, or case studies); participants' characteristics (eg, sample size, age, gender, disorders or symptoms of depression and anxiety, cognitive abilities in terms of Mini Mental State Examination (MMSE) or other cognitive screen scores, and diagnoses or symptoms

of dementia); details of the delivery characteristics of intervention (eg, frequency and duration of treatment, individual or group format, involvement of staff, families, or friends in delivering treatments, additional treatment models); details of the content characteristics of intervention (eg, behavioral activation and cognitive restructuring); and stakeholders' reactions reported in the studies (eg, participants' satisfaction with the intervention, uptake rate, attrition rate, and staff appraisal of the program).

Two independent reviewers will extract data from all the selected studies. Discrepancies between reviewers will be resolved by discussion and consensus, and if necessary, by arbitration of a third reviewer. Furthermore, if additional information is required, we will contact the study authors.

Assessment of Methodological Quality of Included Studies

We will use the Downs and Black [24] instrument, which can be used for randomized and nonrandomized controlled trials, to assess the methodological quality of the included studies. The checklist comprises the following five domains: reporting biases, external validity, biases in the measurement of the intervention and the outcome, biases in selecting participants, and statistical power. In this review, we will report the overall score and the score for each of the domains. Two reviewers will assess all the selected studies. Discrepancies between the reviewers will be resolved by discussion and consensus, and if necessary, by arbitration of a third reviewer.

Data Synthesis

In a table format, we will summarize and present the delivery and the content characteristics of different CBT programs of the included studies. While delivery characteristics refer to how the interventions were approached in residential care settings, the content characteristics refer to the strategies that therapists used with or taught the residents (as detailed above). Furthermore, we will highlight shared components between different programs and components that have been designed particularly for individual groups of residents.

Results

Systematic searches are expected to commence in May 2018. Data extraction is expected to commence in July 2018. Data analyses and writing will happen in October 2018.

Discussion

We will outline the limitations of this systematic review. For example, the studies reviewed might be of poor quality or insufficiently reported to allow for a full audit of relevant variables. Moreover, similar treatments might be labeled inconsistently across studies. We will discuss the clinical implications for treating depression and anxiety in older adults living in residential care settings. Furthermore, we will consider the delivery and content of CBT within such settings to facilitate further development of such treatments across the sector.

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Authors' Contributions

PC and SB devised the protocol. PC wrote the manuscript with inputs from other authors. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy

CENTRAL: Cochrane Central Register of Controlled Trials

CINAHL: Cumulative Index of Nursing and Allied Health Literature

EBSCO: Elton B Stephens CO (company)

ICTRP: International Clinical Trials Registry Platform

MMSE: Mini Mental State Examination

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

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Protocol

A Decision Support System to Enhance Self-Management of Low Back Pain: Protocol for the selfBACK Project

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Abstract

Background: Low back pain (LBP) is a leading cause of disability worldwide. Most patients with LBP encountered in primary care settings have nonspecific LBP, that is, pain with an unknown pathoanatomical cause. Self-management in the form of physical activity and strength and flexibility exercises along with patient education constitute the core components of the management of nonspecific LBP. However, the adherence to a self-management program is challenging for most patients, especially without feedback and reinforcement. Here we outline a protocol for the design and implementation of a decision support system (DSS), selfBACK, to be used by patients themselves to promote self-management of LBP.

Objective: The main objective of the selfBACK project is to improve self-management of nonspecific LBP to prevent chronicity, recurrence and pain-related disability. This is achieved by utilizing computer technology to develop personalized self-management plans based on individual patient data.

Methods: The decision support is conveyed to patients via a mobile phone app in the form of advice for self-management. Case-based reasoning (CBR), a technology that utilizes knowledge about previous cases along with data about the current patient case, is used to tailor the advice to the current patient, enabling a patient-centered intervention based on what has and has not been successful in previous patient cases. The data source for the CBR system comprises initial patient data collected by a Web-based questionnaire, weekly patient reports (eg, symptom progression), and a physical activity-detecting wristband. The effectiveness of the selfBACK DSS will be evaluated in a multinational, randomized controlled trial (RCT), targeting care-seeking patients with nonspecific LBP. A process evaluation will be carried out as an integral part of the RCT to document the implementation and patient experiences with selfBACK.

Results: The selfBACK project was launched in January 2016 and will run until the end of 2020. The final version of the selfBACK DSS will be completed in 2018. The RCT will commence in February 2019 with pain-related disability at 3 months as the primary outcome. The trial results will be reported according to the CONSORT statement and the extended CONSORT-EHEALTH checklist. Exploitation of the results will be ongoing throughout the project period based on a business plan developed by the selfBACK consortium. Tailored digital support has been proposed as a promising approach to improve self-management of chronic disease. However, tailoring self-management advice according to the needs, motivation, symptoms, and progress of individual patients is a challenging task. Here we outline a protocol for the design and implementation of a stand-alone DSS based on the CBR technology with the potential to improve self-management of nonspecific LBP.

Conclusions: The selfBACK project will provide learning regarding the implementation and effectiveness of an app-based DSS for patients with nonspecific LBP.

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KEYWORDS

mHealth; eHealth; case-based reasoning; digital health; machine learning; computer technology; smartphone; primary care; physical activity; exercise

Introduction

Background

The recent Global Burden of Disease Study showed that low back pain (LBP) is the most significant contributor to years lived with disability worldwide [1,2]. Accordingly, LBP is one of the most common reasons for activity limitation, sick leave, and work disability [3,4]. In addition to the suffering of affected individuals, LBP poses an enormous economic burden on society, presenting a huge challenge for health care systems.

selfBACK addresses nonspecific LBP, that is, pain with an unknown pathoanatomical cause, which comprises >85% of all patients with LBP observed in primary care settings [5,6]. In 2006, a European expert working group developed evidence-based guidelines for the management of nonspecific LBP [7,8]; these guidelines have subsequently been adopted and refined by several countries to outline the best practice and appropriate advice to manage LBP [9-13]. Although some variations exist, the main components recommended in the management of LBP include education and reassurance, staying active both in and outside of work, and regular strength and flexibility exercises to prevent relapse, pain-related disability, and chronicity.

Many patients with long-term conditions find it challenging to self-manage their illness, for example, through lifestyle modifications, with little or no additional support [14], and the adherence to self-management programs is commonly poor [15]. Thus, mobile technologies have been suggested as a promising approach to improve self-management of various health conditions [16,17]. In particular, the possibility of delivering tailored support to individual patients has a significant potential with some evidence that tailoring the self-management advice to patients with LBP is more effective compared with nontailoring [18]. Furthermore, increasing evidence suggests that “tailoring” of digital health products is an important factor likely to promote uptake and utilization [19]. However, further research is warranted to clarify how the tailoring of advice for self-management can be integrated and delivered with mobile technologies to promote self-management of LBP. Recent reviews have shown that nearly 300 pain-related mobile phone apps are available [20-23]; however, few of these apps have been developed with evidence-based content and not have they been rigorously tested for effectiveness on pain-related health outcomes [20-23]. Furthermore, health care professionals and patients have seldom been involved in the app development. Thus, a clear need exists for further research aimed at developing high-quality, effective, and smart self-management interventions for LBP [24,25].

In this paper, we outline a comprehensive protocol for the design and implementation of an evidence-based decision support system (DSS), selfBACK, which has the potential to improve self-management of nonspecific LBP. The core of selfBACK is to (1) provide effective evidence-based advice on physical activity and tailored exercise training according to personal goals, personal characteristics, symptom progress, and functional ability and (2) provide educational material to individuals on self-management of their LBP condition. The resulting selfBACK system constitutes a data-driven, predictive DSS that uses the case-based reasoning (CBR) methodology [26-28] to capture and reuse patient cases to suggest the most suitable self-management plan (ie, decision support) for an individual patient. Furthermore, structured intervention mapping will be conducted as an integrated part of the project to guide the design, development, and evaluation of the selfBACK app [29].

Aim and Objectives

The selfBACK project is a Research and Innovation Action funded under the Societal Challenges—Health, Demographic Change, and Well-Being call of the Horizon 2020 program. The project runs from the start of 2016 until the end of 2020. The overall aim of the selfBACK project is to improve self-management of nonspecific LBP to reduce pain-related disability. Figure 1 provides an overview of the project objectives. Phase 1 of the project comprises the development and implementation of the selfBACK system (objectives 1-3) and will run until the end of 2018. Phase 2 of the project comprises a randomized controlled trial (RCT) to evaluate the effectiveness of selfBACK (objective 4).

Objective 1—To Develop an Infrastructure for Collecting and Processing Data

The self-management plan will be tailored to each patient according to data collected by a baseline Web-based questionnaire, a weekly question and answer (Q/A) session in the selfBACK app, and a physical activity-detecting wristband worn by patients. Besides developing an infrastructure for collecting and processing these data, objective 1 also includes work that focuses on the definition of case representations and similarity measures, which are the core components of the CBR technology.

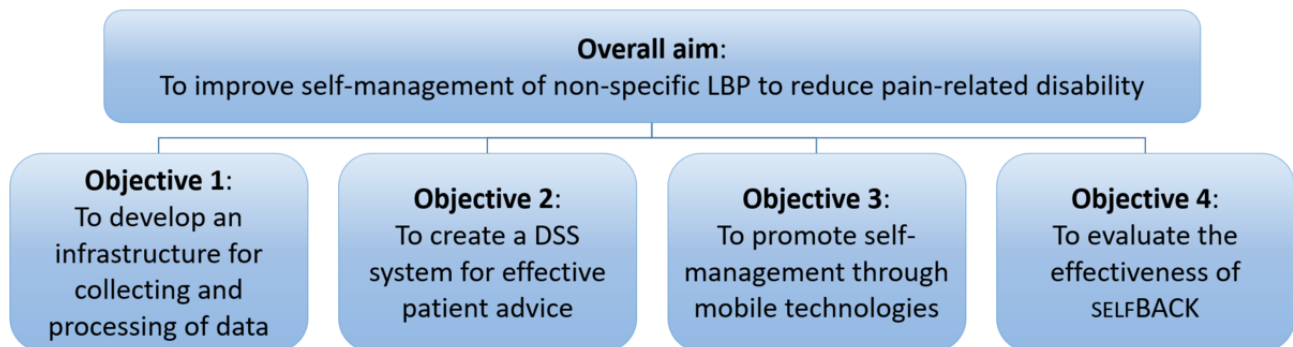
Objective 2—To Create a Decision Support System for Effective Patient Advice

Specifically, the selfBACK system is designed to assist patients in deciding upon and reinforcing the appropriate actions to manage their LBP. Based on the current best evidence, specific content for supporting physical activity, patient education, and strength and flexibility exercises are developed as part of the DSS. Besides CBR for handling situation-specific knowledge,

elements of the model- and rule-based reasoning are used to capture and utilize generalized knowledge (eg, clinical

guidelines) as well as customize the recommendations for self-management.

Figure 1. Overview showing how the overall aim is achieved by the selfBACK objectives. DSS: decision support system; LBP: low back pain.



Objective 3—To Support Self-Management Through the selfBACK App

The decision support is conveyed to patients by a mobile phone app. The app provides patients with (1) instant feedback on the activity level and activity distribution (based on the data stream from the wristband) in accordance with the personal goals set by them and (2) tailored educational sessions and specific exercise training in line with patients' goals, personal characteristics, symptom progress, and functional ability.

Objective 4—To Evaluate the Effectiveness of the selfBACK System

The effectiveness of the selfBACK app will be evaluated in a multinational RCT (parallel group trial) that will target care-seeking patients with nonspecific LBP. The comparator will be patients who receive the usual treatment. In addition, a process evaluation will be carried out as an integrated part of the RCT to document barriers and facilitators for the uptake and utilization of the selfBACK app and for gaining an understanding of patient experiences of using the app. Furthermore, a detailed protocol of the RCT will be reported in a separate publication.

Methods

Concept and Approach

The concept underlying the design of the selfBACK system is that an improved clinical outcome in patients with LBP will rely on behavioral change, which, in turn, might be conditioned by several factors, such as fear avoidance, pain self-efficacy, comorbidities, mood, and physical and mental capacity. The literature offers numerous health behavioral change theories that explain and predict the physical activity behavior, several of which focus on the motivation and volition, in other words, intending to be active and transforming the intention into action [30]. In people suffering from LBP, several factors will affect the relationship between intention and behavior. For example, fear-avoidance beliefs have been demonstrated to affect the activity levels of people with LBP [31,32]. Moreover, it has

been suggested that pain self-efficacy is important in mediating the relationship between pain and functional disability [33], and it has been recognized as one of the main drivers toward positive outcomes [34].

In the following section, we describe the technical solution that will be implemented to address the project objectives and concept underlying the selfBACK DSS.

Components of the selfBACK System

The core of selfBACK is a DSS that helps patients to follow a plan for physical activity (ie, daily step count), education, strength, and flexibility exercises according to personal goals, personal characteristics, symptom progress, and functional ability. To accomplish this, selfBACK incorporates existing knowledge (eg, clinical guidelines and medical ontologies) and information provided by patients to recommend tailored advice for self-management. Figure 2 shows the overall architecture and basic modules of the selfBACK system.

The decision support is conveyed to patients via a mobile phone app in the form of advice for self-management. The app will be developed for Android and iOS using the React Native framework. The process for producing and tailoring the self-management plans and is illustrated by steps 1-6 in Figure 2. Before starting to use the selfBACK app, patients will be required to fill a Web-based questionnaire (1) that provides information about a range of personal characteristics that are used for tailoring the self-management plan (Figure 3, top left quadrant)—this information is fed to the selfBACK server; (2) to initiate the first CBR decision support cycle and produce the first self-management plan, which is pushed to the mobile phone (5) and accessed by patients (6). All further interactions happen via the mobile phone, which collects subjective tailoring data from patients on a weekly basis (4) as well as physical activity data from a wearable (3). The user interaction (4) is a Q/A module used to adjust the weekly self-management plan based on responses to questions on LBP, functional ability, fear avoidance, work ability, barriers for self-management, pain self-efficacy, sleep, perceived stress, mood, and adherence to the self-management plan. The only goal is to ask questions

that are relevant for updating the current decision support for patients and avoiding unnecessary repetition of questions or questions not relevant for the follow-up of a particular patient.

Figure 2. Illustration of the overall architecture and how the data processing of the person-directed modules link together in the selfBACK system.

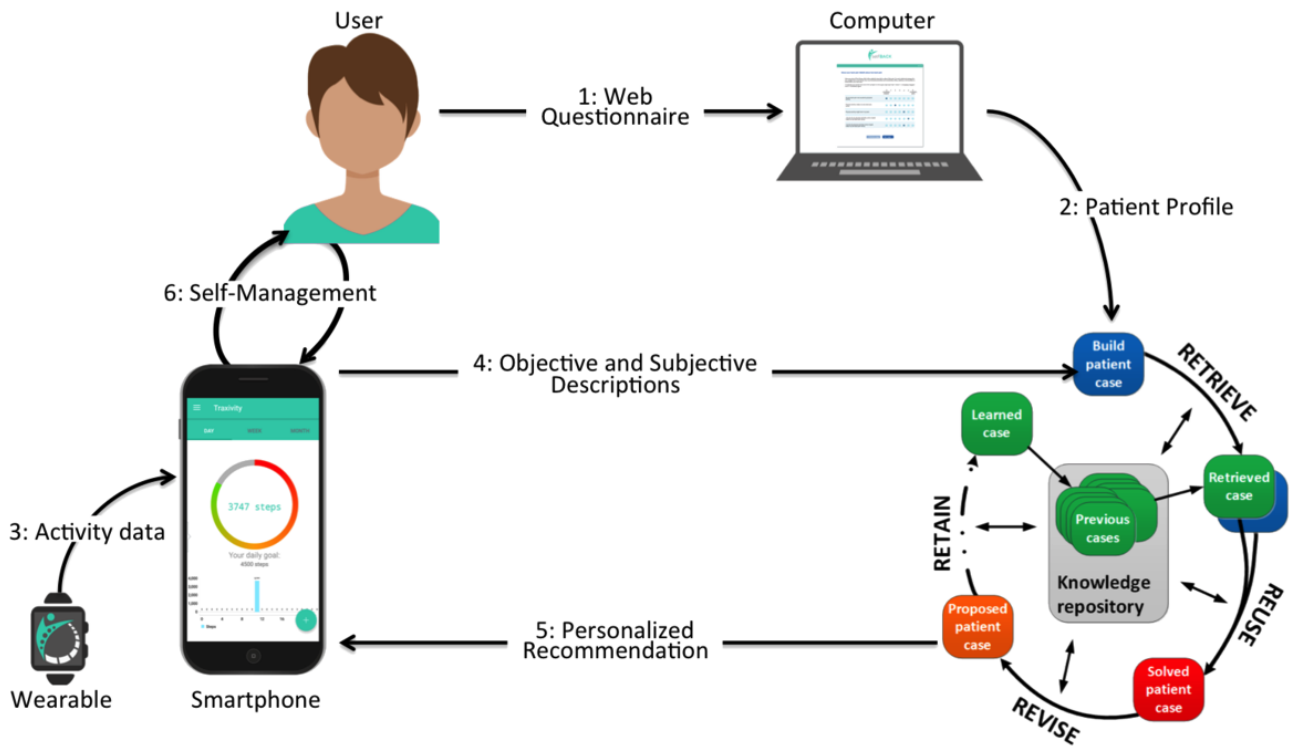
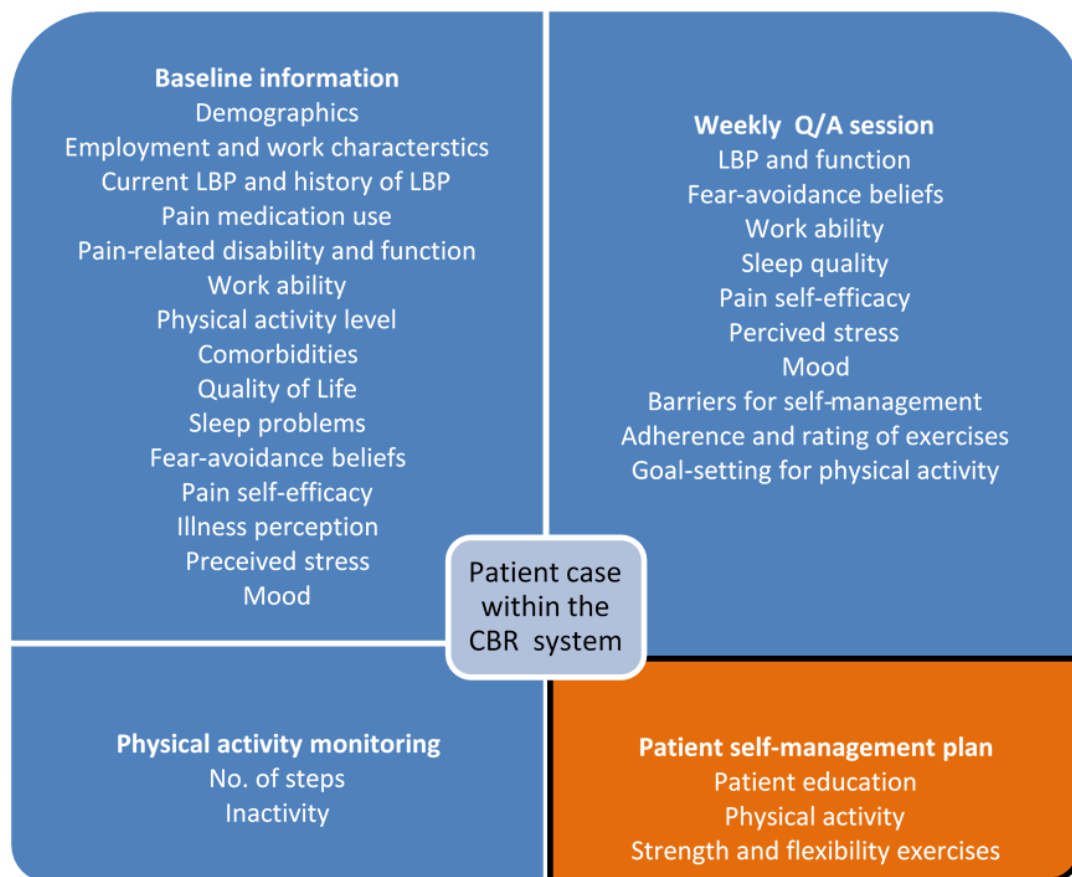


Figure 3. Components of a case description within the case-based reasoning (CBR) system containing the patient characteristics and the compiled advice. Only a relevant sub-set of the weekly questions will be asked in each session. The questionnaires used to collect baseline information are described in Table 1. LBP: low back pain; Q/A: question/answer.



For example, reporting of poor sleep will initiate an educational session targeting sleep behavior accompanied by appropriate follow-up questions. In contrast, reporting of good sleep will reduce the frequency of asking about sleep. Moreover, the regular monitoring of factors such as fear avoidance and pain self-efficacy by the weekly Q/A sessions allows us to make decisions about the amount and type of feedback and educational guidance required by individual users of the selfBACK app. For example, patients with low fear avoidance and high pain self-efficacy may only require simple educational follow-up information provision, whereas patients with high fear avoidance and low pain self-efficacy would require more support and guidance on behavioral change techniques, such as goal setting, pacing, and action planning. In addition, the activity data (3) provide information about whether patients follow the suggestions in the self-management plan (such as the number of steps per day). Regarding the baseline and Q/A data, activity log data are also sent to the selfBACK server giving input to the periodic run of the CBR cycle to generate an adjusted plan for self-management. Furthermore, this means that patients will receive a general advice on physical activity during the first week and that the goal for the number of steps per day will be adjusted in the consecutive weeks according to the incoming data from the wearable.

In addition to the follow-up and feedback on the daily step counts, the selfBACK system provides patients with recommendations on specific strength and flexibility exercises.

The exercise plan conveyed to patients includes instructions and illustrations of the exercises along with recommendations for the number of sessions per week and repetitions or sets within a session. A typical exercise plan is designed to target strengthening of the back extensors, abdominals, gluteal muscles, and core muscles along with the flexibility of knee and hip and trunk muscles with short videos demonstrating the execution of the exercises. At present, insufficient evidence exists to make strong recommendations for or against any specific strength or flexibility exercises [10,35]. Therefore, we will implement a codecision approach where the system suggests an exercise plan that patients can adjust if desired, for example, patients can select exercises they enjoy or feel are beneficial and report on the progression. We hypothesize that this system will increase the adherence to the exercise plan and make it more likely that patients will sustain engagement with the selfBACK app over time. Besides the regular strength and flexibility exercises, the system will recommend pain-relief exercises in the case of a flare-up of symptoms. The latter is part of a "first-aid" kit that patients will have available, which will also include advice about other appropriate measures for acute LBP.

The Decision Support System

The selfBACK system constitutes a data-driven, predictive DSS that uses the CBR methodology to capture and reuse patient cases to suggest the most suitable self-management plan for an individual patient [36]. The CBR cycle includes four processes

that interact with a knowledge repository to suggest a personalized plan for self-management (Figure 2). The data collected by the baseline Web-based questionnaire, the Q/A session, and the wearable are formatted to match existing representations. Hence, we will build an individual patient case from this data, which subsequently would be matched with the existing case base (RETRIEVE). Then, the best matching case will be selected to be fitted to the current patient (REUSE). A core method in the retrieval step is similarity assessment, which compares how similar cases are to each other on demographic, pain, and mood-related information. After retrieving a similar past successful case, a plan for self-management will be adapted to the current case. This process is guided by a set of adaption rules and the goals set by patients. The result is a personalized and individually tailored self-management plan for patients. The plan is fetched from the server by patients' mobile phones as an *active case* and monitored over the planned time period. In addition, the REVISE step in the CBR cycle addresses the evaluation and possible revision of the output from REUSE before learning from the new case takes place. In the selfBACK system, this step is not performed at once but rather postponed until the effect of the system's currently suggested plan (ie, the output from REUSE) can be assessed. At that time, patient's case might be stored as a new case in the knowledge repository (RETAIN). Furthermore, the case can be temporarily stored in a preliminary case store, where all cases whose effects have not yet been evaluated are kept. In general, all cases stored in the

knowledge repository (learned cases) are available for subsequent development of self-management plans and activity suggestions, thus restarting the CBR cycle.

Figure 3 describes the data sources and the structural contents of a case in the selfBACK's CBR system. The accompanying Table 1 provides an overview of the information collected at the baseline that was fed into the selfBACK DSS. The case consists of a patient's description and matching self-management plan. Data for the patient's description are acquired with different frequencies in the selfBACK lifecycle, and the self-management plan is updated accordingly. A substantial part of the information obtained at the baseline is static (eg, demographics), whereas other information is expected to vary over time and hence, will be updated on a regular basis through the Q/A session (eg, pain-related disability and function). In addition, the selfBACK system uses data abstractions, rather than raw data, for comparing cases. Each case in the case base is structured as illustrated in Figure 3. Every query is represented in the same way as a case but without a self-management plan; this is referred to as an input case. For the similarity-based comparison between an input case and past cases, the DSS runs three parallel services, which are as follows: (1) one taking all physical activity features into account to suggest activity goals; (2) the second service taking all strength and flexibility exercise features into account to suggest a new exercise program; and (3) the third service takes all relevant education features into account to suggest new education sessions.

Table 1. Overview of the information collected at the baseline.

Baseline information	Response options or questionnaire reference
Demographics	Age, gender, height, weight, family, ethnicity, education, employment status
Physical work characteristics	Saltin–Grimby Physical Activity Scale [37]
Current LBP^a	
Average last week	Visual analog scale, 0-10 [38]
Worst last week	Visual analog scale, 0-10 [38]
History of LBP	
Length of current episode	<1 week; 1-4 weeks; 5-12 weeks; >12 weeks
Days with LBP past year	0 days; 1-7 days; 8-30 days; >30 but not every day; every day
Use of pain medication last week (days)	None; 1-2 days; 3-5 days, daily
Pain-related disability	Roland-Morris Disability Questionnaire [39]
Function	Patient Specific Functional Scale [40]
Activity limitation	
Reduced work activity	Yes; no
Reduced leisure time activity	Yes; no
Current work ability	Work ability index, 0-10 (single item) [41]
Leisure time physical activity	Saltin–Grimby Physical Activity Scale [37]
Comorbidities, musculoskeletal	Pain mannequin
Comorbidities, others	Cardiovascular disease; heart failure; stroke or brain hemorrhage; asthma; chronic bronchitis or emphysema, COPD ^b ; diabetes; gastrointestinal problems; kidney disease; cancer; epilepsy; osteoporosis; osteoarthritis; depression; anxiety; sleep apnea; rheumatoid arthritis; psoriatic arthritis or psoriasis; other
Quality of life	EQ-5D ^c [42]
Sleep problems	Sleep Screening Questionnaire [43]
Fear-avoidance beliefs	Fear-Avoidance Beliefs Questionnaire [44]
Pain self-efficacy	Pain-Related Self-Efficacy Questionnaire [45]
Illness perception	Brief Illness Perception Questionnaire [46]
Perceived stress	Perceived Stress Scale [47]
Mood	Patient Health Questionnaire [48]

^aLBP: low back pain.

^bCOPD: chronic obstructive pulmonary disease.

^cEQ-5D: European Quality of Life-5 Dimensions.

The selfBACK Architecture

The selfBACK architecture consists of clients that are connected to a server, which holds the DSS. The architecture covers the following two main scenarios. First, a patient is provided with the necessary credentials to access a web interface to be used for the initial sign-up and to fill out a baseline questionnaire, and second, a patient is equipped with a wearable and the selfBACK mobile phone app, which guides self-management according to the goals set by the patient. The mobile phone app synchronizes with the wearable and obtains the patient's activity log and sends push notifications with content that encourages physical activity. Furthermore, the mobile phone app itself is the tool for the patient to obtain personalized information and educational explanations.

The decision support server performs all relevant tasks for maintaining the knowledge repository and provides the infrastructure for the advice generation services. Those services are parts of the server and communicate with clients through a secure access layer. The data generated will be used for updating each patient's self-management plan.

The clients are either native mobile phone app or web browser users accessing the selfBACK system. The server can only be accessed through the secure access layer, which requests authentication and maintains user groups and secure workflows ensuring only relevant data are accessible to any client. In addition, the decision support server performs all relevant tasks from preprocessing incoming data and creating abstractions to running the decision support engine; this process is enhanced by machine learning tasks, which enable the creation of new cases and rules from incoming data. The knowledge obtained

from this process is stored permanently in the knowledge repository.

The core of the DSS is the CBR system for finding the most similar patient cases. An additional rule-based system module captures generalized knowledge that is complementary to the situation-specific knowledge in cases in the form of clinical guidelines and generalizations over cases. Depending on its type, each incoming data stream is preprocessed in a particular way. In addition, data abstraction enhances the incoming data with domain knowledge, thereby allowing more comprehensive reasoning to support the decision making. Furthermore, implementing case matching as software services allows selfBACK to scale and perform the generation of self-management plans in parallel, whereas the core engine and knowledge repository stay consistent.

The knowledge repository holds cases and rules as well as the underlying ontology, and provides this knowledge for the DSS. The case base, containing cases, is the primary source of knowledge. Rules provide additional knowledge, particularly targeted for representing relevant clinical guidelines and knowledge. Furthermore, the ontology defines the concepts used by cases and rules with essential relations such as the taxonomical relations that enable the inheritance inference within the ontology.

Data Processing in selfBACK

Preprocessing is performed on all data sources, which are included in the target knowledge models. Data are structured and grouped according to the domain and information types using the ontology. In addition, incoming data are cleaned, normalized, and transformed, and the significant features and instances are selected. The preprocessing strategy depends on the source data and its purpose in the knowledge model.

Data abstraction is applied to make data streams comparable and prepare data for the next process, the personalized decision support. selfBACK uses existing state-of-the-art methods for detecting trends in raw data. In addition, the individual activity streams are processed to reduce complexity or enhance them with the information required for better matching. Once data are delivered to the DSS, each patient is represented as a self-management agent who uses the incoming data to build up a query (a case with a problem description only) and match it against the case base. Consequently, it receives the best matching case that is subsequently personalized to give appropriate advice, enhanced with explanations. Then, an updated self-management plan is returned to the user. Explanations might be justifications for the advice, that is, “how was this advice derived?,” and an explanation of the effects of the advice given the current situations of patients. Furthermore, explanations are stored as predefined text elements in a separate part of the knowledge repository.

Structured Intervention Mapping and User Involvement

In this study, structured intervention mapping is used to guide the development of the content for the selfBACK system [29]. Importantly, structured intervention mapping promotes a strong theoretical underpinning of the logic model of an intervention.

In selfBACK, the logic model is underpinned by behavioral change theories [49] and the normalization process theory [50] to help us understand and evaluate the factors that promote or inhibit the uptake, utilization, and sustained use of the selfBACK app. Moreover, developing selfBACK through the involvement of users and key stakeholders (ie, patients and clinicians) maximizes sustainability and empowerment, increases commitment to the intervention, and increases credibility and likelihood of the uptake and utilization of the intervention [29]. In addition, direct input from patients, through primary research methods like observation, interviews, and focus groups, provides insights into users' behavior, including what they want to do with the selfBACK app, how the selfBACK app is integrated into their living environment, when and how they will use it as well as the perceived barriers and facilitators of utilization (drop-off and retention factors).

Throughout the development of the selfBACK DSS, patients with LBP and health care professionals have been interviewed and asked about their experience with the traditional treatment of back pain and how they usually self-manage their LBP. In addition, a panel consisting of clinicians (eg, physiotherapists, chiropractors, sports physiologists, and psychologists) provided feedback and answered a survey concerning the choice of physical exercises and the educational content. Furthermore, the selfBACK team members (eg, physiotherapists, chiropractors, exercise physiologists, and medical doctors) contributed to group discussions and the structuring of the content implemented in the selfBACK DSS. Finally, the developmental versions of the selfBACK app are continuously tested by patients and team members in iterative rounds, during which information is collected in interviews and group sessions with potential users.

Results

The selfBACK project was launched in January 2016 and will run until the end of 2020. The version of the selfBACK DSS that will be used in the RCT will be completed in the fall of 2018. Our target population is care-seeking patients in primary care settings diagnosed with nonspecific LBP. Clinicians will identify patients who will be eligible for self-management and participation in the RCT. The recruitment of patients and data collection in the RCT will start in February 2019 with pain-related disability at 3 months as the primary outcome with additional follow-ups at 6 weeks, 6 months, and 9 months. In addition, results for the trial will be reported according to the CONSORT statement [51,52] and the extended CONSORT-EHEALTH checklist [53]. Along with publications in peer-reviewed scientific journals, the results will be disseminated to a wider audience and key stakeholders, such as patient organizations, health care professionals, and relevant policy makers, through social media and other mechanisms. Moreover, market introduction and exploitation of the results will be based on a business plan developed by the selfBACK consortium and will be ongoing throughout the project period with a strong focus toward the mobile health (mHealth) technology industry. The methodology that is being developed is expected to have wide applicability to other chronic conditions with similar conceptual elements.

Discussion

Nonspecific LBP is a condition with large interindividual variation in symptoms, treatment responses, and outcomes and is, therefore, suitable for personalized care. Recent studies have shown that a stratified care approach for LBP results in a substantially better treatment response compared with treatment as usual [54,55] as well as the cost-effective use of health care resources [56]. The selfBACK project goes beyond the current state-of-the-art by developing a DSS that reinforces the patients' motivation for self-management by providing a personalized plan for self-management and real-time feedback on the achievement of personal goals. Of note, the selfBACK approach is the first example of a DSS that utilizes CBR technology to tailor self-management plans for a patient with LBP.

In selfBACK, we will collect data about patients by a baseline Web-based questionnaire, an activity-detecting wearable, and weekly Q/A sessions in the selfBACK app. The obtained information will be used to personalize advice to optimize and reinforce self-management of nonspecific LBP. In addition, the collected data, along with the personalized plans for self-management, will be used to build and add new cases to the system's knowledge repository. The system's automatic learning component enables new knowledge and plans for self-management to be integrated into the system's knowledge repository, whereas experiential case-based learning enables improved patient support over time. Therefore, the selfBACK system is a powerful tool to facilitate, improve, and reinforce self-management of nonspecific LBP. Furthermore, the use of the selfBACK app does not require direct medical supervision and can easily be made available to a large number of people implying a cost-effective use of resources. However, selfBACK is not intended to replace clinical care, and we will adhere to the Health On the Net Foundation (HONcode) principle [57], a code of ethics that specifies certain requirements for the quality of digital patient support. Moreover, the selfBACK system will be certified according to these principles before it is launched to users.

The educational and supportive material, general physical activity, and specific strength and flexibility exercises constitute the main components of LBP self-management. In selfBACK, the patients' physical activity level is monitored and followed-up by data provided by an activity-detecting wearable. The wearable stores data for future synchronization and users do not need to have the phone connected at all times. The monitoring of physical activity will be accompanied by motivational textual feedback displayed on the mobile phone screen. Based on the available sensors embedded in the wearable (eg, three-axis accelerometer), different health metrics are derived, including the number of steps taken and the duration of inactivity. Moreover, we can derive the time a patient is not wearing the wearable to indicate the user pattern of the selfBACK system. Although recent studies have indicated that

wearables have poor validity in estimating the energy expenditure [58,59], they have acceptable reliability [60] and validity for the step detection [61], thereby fulfilling our requirement, that is, repeated daily measurements of steps in the same individual.

Many patients find it challenging to self-manage their illness with little or no additional support and the adherence to self-management programs is commonly poor [14,15]. With the selfBACK app, we envisage that the problems of feedback, reinforcement, and the adherence to self-management can be solved by offering an evidence-based system that allows personalized follow-up and advice to patients, thereby enhancing the motivation and perception of usefulness. This speculation is supported by findings from persuasive technology research showing that the adherence to home-based exercise and self-management increases when patients receive personalized feedback, perceive the advice as evidence-based, receive reminders to stay active and exercise, and know that their adherence is being monitored [62,63]. Furthermore, empowering patients toward "self-regulatory" behavior by personal goal setting and self-monitoring increases the adherence and effectiveness of an intervention [64]. Therefore, we envisage that selfBACK will be more effective and motivating compared with the current treatment model, wherein patients are generally unsupported when self-managing nonspecific LBP.

A strength of the selfBACK approach is the strong theoretical underpinning along with the use of data-driven computer modeling to tailor advice and follow-up on self-management. Furthermore, because the advice is grounded in the system's growing experience on the effect of plans for self-management and the accompanying symptom progression, the prediction quality of selfBACK will increase over time. Thus, the selfBACK app could potentially become a potent tool for supporting self-management in patients with LBP. Nevertheless, the risk of poor engagement or the lack of sustained participation exists. Importantly, a process evaluation will be conducted along with the RCT, enabling us to document the implementation of selfBACK, including patient experiences of using the app. This will provide clues about how patient-centered DSSs, such as selfBACK, should be designed to maximize uptake and utilization.

By adapting and advancing the state-of-the-art technology in data capture, data analysis, and proactive decision support, we will, in the selfBACK project, develop and document a DSS to be used by patients themselves to support self-management of nonspecific LBP. In line with current evidence-based recommendations and guidelines, selfBACK incorporates physical activity, education, and specific strength and flexibility exercises to improve, facilitate, and reinforce the self-management process. Furthermore, the effectiveness of selfBACK will be evaluated in a multinational RCT, targeting care-seeking patients in a primary care setting.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Evaluation Summary Report from the European Commission.

[[PDF File \(Adobe PDF File\), 115KB - resprot_v7i7e167_app1.pdf](#)]

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Abbreviations

CBR: case-based reasoning

CONSORT: consolidated standards of reporting trials

CONSORT-EHEALTH: consolidated standards of reporting trials statement for randomized controlled trials of electronic and mobile health applications and online telehealth

COPD: chronic obstructive pulmonary disease

DSS: decision support system

EQ-5D: European Quality of Life-5 Dimensions

HONcode: Health On the Net Foundation

LBP: low back pain

RCT: randomized controlled trial

Q/A: question/answer

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Protocol

Technology-Enhanced Consultations in Diabetes, Cancer, and Heart Failure: Protocol for the Qualitative Analysis of Remote Consultations (QuARC) Project

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Abstract

Background: Remote videoconsulting is promoted by policy makers as a way of delivering health care efficiently to an aging population with rising rates of chronic illness. As a radically new service model, it brings operational and interactional challenges in using digital technologies. In-depth research on this dynamic is needed before remote consultations are introduced more widely.

Objective: The objective of this study will be to identify and analyze the communication strategies through which remote consultations are accomplished and to guide patients and clinicians to improve the communicative quality of remote consultations.

Methods: In previous research, we collected and analyzed two separate datasets of remote consultations in a National Institute for Health Research-funded study of clinics in East London using Skype and a Wellcome Trust-funded study of specialist community heart failure teams in Oxford using Skype or FaceTime. The Qualitative Analysis of Remote Consultations (QuARC) study will combine datasets and undertake detailed interactional microanalysis of up to 40 remote consultations undertaken by senior and junior doctors and nurse specialists, including consultations with adults with diabetes, women who have diabetes during pregnancy, people consulting for postoperative cancer surgery and community-based patients having routine heart failure reviews along with up to 25 comparable face-to-face consultations. Drawing on established techniques (eg, conversation analysis), analysis will examine the contextual features in remote consultations (eg, restricted visual field) combined with close analysis of different modes of communication (eg, speech, gesture, and gaze).

Results: Our findings will address the current gap in knowledge about how technology shapes the fine detail of communication in remote consultations. Alongside academic outputs, findings will inform the coproduction of information and guidance about communication strategies to support successful remote consultations.

Conclusions: Identifying the communication strategies through which remote consultations are accomplished and producing guidance for patients and clinicians about how to use this kind of technology successfully in consultations is an important and timely goal because roll out of remote consultations is planned across the National Health Service.

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KEYWORDS

remote consultations, communication, language, linguistics, cancer, diabetes mellitus, heart failure

Introduction

Background

Health services face rising costs because of increasing disease prevalence, high “did not attend” (DNA) rates, and poor patient engagement, resulting in poor health outcomes and greater use of emergency care [1,2]. Most outpatient models fail to reliably provide responsive care when patients need intervention. The search is on for new and affordable ways of delivering care, particularly for those with chronic illnesses. Current national-level policy places considerable faith in digital technologies and their potential to deliver more efficient, effective, and patient-centric care [3-6]. Digital technology plays a significant, though varied, role in health system plans in reconfiguring hospital services and transforming the delivery of health services [7]. Attending regular clinics can be expensive, physically challenging, and inconvenient for patients [8]. Remote consultations (using Skype or similar applications) have the potential to fundamentally change the way in which patients interact with clinicians. However, the Web-based environment is known to produce subtle alterations in the dynamics of human interaction, potentially increasing the risk that clinical clues will be missed or the clinician-patient dynamic will be altered adversely [9,10]. As a radically new service model, it also carries operational and interactional challenges, including providing technical support, training staff and patients in using digital technologies, and avoiding potential for misunderstandings when (potentially sensitive) information is transferred remotely.

The current evidence base on remote consultations is sparse but has begun to develop [11-20]. A 2015 review identified 27 published studies that used Skype and similar technologies in clinical care, all but one of which reported positive benefits [12]. Most of these studies, and those published since [8,17,21-24], are brief descriptions of small pilot-stage projects or use experimental methods, especially randomized controlled trials (RCTs), to compare the remote option with traditional face-to-face encounters. Many of these studies focus on the use of Skype to support remote consulting with fewer examining other options, for example, FaceTime, Whatsapp, or purpose built applications [25]. A small number of studies examine combinations of technologies, for example, use of Skype plus texting [26] or use of remote consultations plus monitoring [27]. However, despite reported benefits, for example, in terms of increased access for patients [9,28-30], particularly those with complex needs [31], patient and clinician satisfaction with the remote option [23,32-35], potential time and cost savings [8,36,37], improvement in self-management skills [38], and improved compliance to treatment and/or clinical outcomes [17,22,24,31,39-43], small sample sizes (eg, 5 patients), and high losses to follow-up prevent any unqualified conclusions that remote consultations are “effective.”

In many published studies, technical and communication issues are mentioned but are not explored in depth. A number of studies have focused on the patient-provider relationship and concluded that there is little, if any, difference when comparing remote consultations with usual face-to-face care [44]. One study

focused on the strength of the relationship among patients, caregivers, and health care professionals when behavioral health care was provided for adolescents with poorly controlled type 1 diabetes mellitus [45]. They concluded that the therapeutic relationship was similar to clinic-based care (on the basis of both adolescent and parent reporting via a survey) and that the relationship or care provided was largely unaffected by remote consulting. The research did not include close examination of communication or the role of technology.

There is recognition in the literature of the potential effects of remote consulting on satisfaction, adherence and compliance, health and clinical status, recall and understanding, and psychological well-being in the context of health care consultations [46,47]. There is currently limited published research that explores such potential effects. There is extensive evidence focusing on communication and interaction in health care consultations, highlighting how communication is shaped by wide ranging factors, such as patient preferences and available time [48-50], patient and clinician ethnicity, gender, behavior, and orientation to patient-centered care [50-53], interpretation (eg, of parental requests for further information) [54], nonverbal communication [55], and the use of technology (eg, electronic patient records) [56-58]. To our knowledge, there are no studies reporting the impact of remote consulting technology on communication and interaction in medical consultations. We found 2 studies that examined the quality of communication in the context of telemedicine consultations, one with primary care providers and patients consulting with specialists across a range of conditions using modular video/audio systems at either end [59] and the other with older patients requiring pulmonary medicine consultations and using a live 2-way audio and videoconferencing service [60]. Findings from both papers suggested that the use of telemedicine influences communication with doctors more likely to dominate telemedicine consultations. To our knowledge, there have been no papers examining the quality of communication in the context of Skype or similar Web-based media. Studies beyond the medical literature highlight the ways in which such media might alter interaction, for instance, by subtly desynchronizing communication [61,62]. There are questions about whether technical failures (eg, connecting but hearing no sound), new communicative foci (eg, “talking heads,” showing digital objects), new types of greetings (eg, the opening sequence of a video meeting), or interruption (eg, a family member entering the room) impact the consultation [62-68]. This evidence has yet to be considered in relation to remote medical consultations. We are still unaware how different communication strategies, modes of communication (speech, bodily conduct, gaze, and posture), and/or the material properties of the technology shape and constrain interactions in remote consultations.

Our Research on Remote Consultations to Date

The Qualitative Analysis of Remote Consultations (QuARC) project, which is described in this paper, builds on previous research by our team, especially the Diabetes, Review, Engagement and Management via Skype (DREAMS) study, funded by the Health Foundation from 2012 to 2014, the Virtual Online Consultations-Advantages and Limitations (VOCAL) study, funded by the National Institute for Health Research

(NIHR) Health Services and Delivery Research program from 2015 to 2017, and the Oxford Telehealth Qualitative Study (OTQS), funded by the Wellcome Trust as part of a wider program of research undertaking Studies of Co-creating Assisted Living Solutions from 2015 to 2020.

VOCAL was a multilevel qualitative study on remote (“Skype” and similar) consultations involving macro level data (on national policy and industry strategy relating to remote consultations), meso level data (on organizational tasks and processes), and micro level data (videotaped consultations). Combined with the findings of DREAMS (an earlier, smaller study in the same setting), these findings showed that remote consultations appeared safe, effective, and convenient for patients who were preselected by their clinicians as “suitable” (although such patients represent a small fraction of clinic workloads) and were associated with improved DNA rates, reduction in Accident & Emergency attendance, improvements in blood glucose control, increased patient satisfaction, and lower patient-borne costs [19,69].

OTQS is a qualitative case study exploring telehealth and videoconsulting in patients with heart failure in the context of a large, UK-wide RCT. Study results indicate that most patients are judged “unsuitable” for remote consultations by clinicians or preferred to be seen face-to-face (in part because patients with heart failure have frequent comorbidities and are often frail, making their care complex and the course of their condition unpredictable). Despite these issues, there are remote consultations that patients and clinicians describe as “successful,” in which much of the focus is on lifestyle aspects of the condition (eg, questions about exercise tolerance and sleep quality, which indicate both physiological status and functional consequences) and medication compliance. We have observed successful discussions about medication, including a nurse identifying and correcting a misunderstanding of what dose of medication to take. We have also observed heart failure nurses successfully talking patients and/or relatives through self-examination of ankle edema and blood oxygen and blood pressure testing.

The combined dataset obtained from VOCAL and OTQS recordings offers opportunities for addressing questions about communication and quality of care in remote consultations. Preliminary analysis of the videos and transcripts across both studies suggests that remote consultations have advantages (eg, patients generally feel satisfied and many prefer consulting from the comfort of their own homes with family around them; clinicians who regularly use Skype or similar media are keen on this medium) but that they are different (eg, compared with the equivalent face-to-face encounter the overall length is shorter), even when taking account of the small amount of “technical talk” at the beginning (eg, “can you see me?” or “is the video on?”), and the flow of conversation is less natural [18]. In remote and face-to-face consultations, clinicians did more talking and exerted more control. One difference that was statistically (and probably clinically) significant was that both parties sometimes needed to state things explicitly in a remote consultation that remained implicit (and/or obvious to both parties) in a traditional face-to-face encounter. We also observed several examples of technical failure, including human error

(eg, forgetting passwords) that significantly interfered with the quality of the consultation, with patients or staff not always sufficiently skilled or confident to undertake the necessary “troubleshooting” to achieve and maintain the video connection. More detailed methods and analysis from the VOCAL study can be found in the study report [70] and main findings paper [18].

To summarize, the existing evidence suggests that there is great potential for the use of Web-based media tools, such as Skype, for remote communication between patients and clinicians. However, while studies are broadly positive, the select nature of samples, small sample sizes, and high losses to follow-up raise questions about conclusions that the technology is “effective.” Literature, specifically on remote consultations, is currently limited. The contribution of Web-based media to consultations in health care has been studied mainly using experimental methods, especially RCTs, which have generally focused on evaluating the outcomes of the technology. There is extensive evidence focusing on the communication and interactions in medical encounters, for example, Stivers and colleagues [71], Stevenson [50] and Robinson [72], but none that examines the detail of interaction when consultations take place remotely. Evidence from studies beyond the medical literature highlighting the ways in which Skype and similar media might alter interaction (eg, desynchronizing communication) has yet to be considered in relation to remote consultations. In short, there is a significant knowledge gap in relation to the fine detail of communication in remote consultations. Addressing this gap and producing guidance for patients and clinicians about how to use this kind of technology successfully in consultations is an important and timely goal because roll out of remote consultations is planned across the National Health Service (NHS).

Methods

Aims

To identify and analyze the communication strategies through which remote consultations are accomplished and produce guidance for both patients and clinicians for improving the communicative quality of remote consultations.

Objectives

Our objectives are as follows:

1. To analyze a multimodal dataset of up to 40 remote consultations with patients diagnosed with diabetes, cancer, and heart failure, and their clinicians (and compare these with a subset of up to 25 audio-recorded face-to-face consultations) using a combination of ethnographic and microanalytic approaches to investigate, in detail, how interactions are affected by mediation via Skype or similar applications
2. To generate findings on the detailed dynamics of communication and interactions in remote consultations and bring patients and clinicians, who have been involved in remote consultations together for a consolidating learning workshop to gather feedback and develop/refine resources

3. To develop provisional guidance for patients and clinicians on conducting remote consultations (provisional in the sense that study design does not allow conclusions to be drawn across all clinical areas)

Research Questions

This study will examine the following research questions:

1. What are the (often implicit or unspoken) communication strategies through which technology-mediated consultations for diabetes, cancer, and heart disease are successfully accomplished?
2. How do patients and clinicians address misunderstandings in technology-mediated consultations and what strategies are more effective?
3. What can we learn from detailed linguistic analysis of real-life remote consultations to guide other clinicians and patients interested in or actively using Skype and other social media?

Overview of Study Design

NIHR and the Wellcome Trust separately funded studies to collect data on remote consultations with doctors and nurses. This study will combine multimodal data (video, audio, and screen captures at both “ends” of a remote consultation) from these 2 (independently conducted) studies involving up to 40 remote consultations and comparing these with a subset of up to 25 face-to-face consultations and analyze the interaction using techniques designed for fine-grained analyses of verbal and nonverbal interactions. This powerful technique has yet to be applied to remote consultations, partly because of the logistical difficulties of obtaining high-quality video and audio data at both ends of a consultation.

Theoretical and Conceptual Framework

Findings from our own, and others, research highlight important interactional differences between remote and face-to-face consultations (see above) and indicate that the mode of communication can alter the interpersonal dynamics between patients and clinicians [10,18,19]. To examine the significance of this, we will make use of both long-established techniques developed for microanalysis of face-to-face and telephone conversations [73,74] and insights from recent work on mediated and multimodal interaction using both verbal and visual channels, for example, videoconferencing, vlogging, and courtroom video links [62,67]. We will use 2 complementary theoretical approaches that see communication as a dynamic interaction that emerges moment by moment and look beyond the traditional patient/clinician dyad to examine the role of technology in shaping interaction.

First, we will use the “ethnography of communication” (an approach that aims to produce systematic and richly contextualized descriptions of the communicative genres, events, and practices that are observed in a particular culture [75]) to identify the key features of remote consultations and attend systematically to the contextual factors (eg, lack of spatial proximity and restricted visual field) that may be producing differences with face-to-face consultations. Our focus will be on “communicative competence” [76] (ie, how participants in

remote consultations deploy their tacit understanding of a particular communicative event and what competencies are needed to maximize the benefits of the encounter).

Second, we will use discourse analysis to guide fine-grained examination of the patterning of interaction at a “micro”-level (ie, how consultations are managed by participants moment by moment). Discourse analysis encompasses a number of approaches [77]. We will draw on concepts and techniques from several of these, including Conversation Analysis, which focuses on the resources used by participants in talk to create/maintain order and coherence [78-80], interactional sociolinguistics, which focuses on the use of context-specific frames and schemas to negotiate meaning in interaction [81], and multimodal discourse analysis, which focuses on the interaction of different modes and channels of communication, for example, verbal and visual, to produce meaning, especially in mediated environments [10].

Setting

Data will be drawn from 2 independently conducted studies on remote consultations.

Setting 1

The VOCAL study (March 2015-July 2017) was undertaken with Barts Health, the UK’s largest acute trust. We studied 2 services, Diabetes and Pancreatic/Liver Cancer, both based in London boroughs characterized by high socioeconomic deprivation and ethnic and linguistic diversity. Barts Health is under pressure to deliver services more cost-effectively while responding to rising need and demand. Extending remote consultations is a part of that plan. The Diabetes Service (led by SV) has a tradition of ensuring that services are accessible and oriented to meeting the needs of the most vulnerable and serves a population with one of the UK’s highest prevalence of type 2 diabetes in the 16-25 age group. Engagement with traditional health service models is low. Remote consultations, where clinically appropriate, appear to be acceptable allowing for a flexible model of care. Experience delivering remote consultations since 2012 suggests they are popular with patients and staff.

The Royal London Hepato-Pancreato-Biliary Cancer Service (led by SB) is a tertiary service, which patients often travel long distances (up to 200 miles) to access. It provides contrasting demographic and clinical challenges to the diabetes example. Patients with pancreatic and liver cancer have a diverse demography but have in common a life-threatening diagnosis, major surgery, and a prolonged postoperative phase, in which they have to cope with multiple physical, emotional, and practical challenges. The service has been trialing remote consultations (largely for postoperative follow-up) since September 2015.

Setting 2

The OTQS study (on-going) is undertaken with the community-based, specialist nurse-led service funded by Oxford Health NHS Foundation Trust and working in liaison with the hospital-based heart failure service, local GPs, other community services (eg, palliative care nurses), integrated locality teams

(occupational therapy, physiotherapy, mental health), social services, and 5 locality-based ambulatory assessment units providing emergency care for patients. The community heart failure nurses each have an active caseload of 100-120 patients, which they manage through a combination of community clinics, home visits, and telephone management. A high proportion of patients are unable to get to clinic (owing to frailty or fatigue) and home visits are time-consuming. Consequently, the remote option is a viable alternative. The team remains keen to evaluate whether remote consultations can help them deploy their limited resources safely, efficiently, and effectively without loss of patient or staff satisfaction. Some clinicians (particularly nurses) are skeptical because the functional and cognitive deficits in many patients with heart failure present a challenge to remote consulting.

Cross Study Sample

We will include all of the remote consultations recorded in both studies. This currently gives a sample of 39 remote consultations (Table 1). We plan on collecting one more remote consultation in the heart failure service, raising the overall total to 40.

The goal of sampling has been to capture the breadth of (patients' and staff's) experience of remote consultation. The number of patients with cancer and heart disease is lower because there are greater practical and ethical challenges to gaining informed consent and avoiding harm, particularly in cases of heart failure which often require physical examination.

Within each subsample we have sought maximum variety in clinical, social, ethnic, and personal circumstances. In the diabetes service, we sought to include young adults, older people, limited English speakers, and women who recently had diabetes in pregnancy, all of whom, for various reasons, struggled to engage with the regular service. Our sample for cancer was drawn from a tertiary care surgical center and included those receiving postoperative follow-up and posttreatment surveillance. In the heart failure service, we sought patients with left ventricular systolic dysfunction or heart failure with preserved ejection fraction under the care of a cardiologist and those identified by the heart failure specialist nurses (tasked with educating newly diagnosed patients, up-titrating medications, and monitoring benefits or adverse effects of medication) as suitable for remote consultation. Further detail on sampling and the context in which consultations took place can be found in previous study reports [18,70]. Because remote consulting is a new medium with potentially harmful effects in

some patients, patient participants were selected for invitation based on the clinician's judgment from the denominator population of all those attending participating outpatient clinics. Exclusion criteria were no 3G access (VOCAL), or no 3G or Wi-Fi (OTQS) at home, lack of familiarity with the relevant technology, clinical inappropriateness (eg, need for physical examination), inability to give informed consent, and comorbidity preventing participation (eg, severe visual impairment).

To enable comparison, we collected 17 audio recordings of matched face-to-face consultations with patients diagnosed with diabetes, cancer, and heart failure. Additionally, we plan to collect a further 8 (giving a total of 25) face-to-face consultations, matched as closely as possible for the type of condition, type of appointment (eg, 6-month follow-up), patient demographics (eg, gender, ethnicity) and, in all cases, for the clinician.

Description of Study Dataset

The core dataset of (currently 39, planned 40) video-recordings of remote consultations incorporates video, audio, and screen capture at both "ends," clinician and patient, for each consultation along with detailed transcriptions.

Both studies captured 2 video streams, what the clinician sees and does in the clinic and what the patient sees and does at the remote site (the place where the patient consults from, typically, from the living room at home). To date, in 27 of the 39 consultations, we have recorded the clinician's end of the consultation using a small digital camcorder. We used the same or equivalent technology for the patient end to capture video and good quality voice recordings. In each of the consultations, the camera's field of view captures as much as possible of the individual and their orientation toward the screen (eg, a computer or tablet) as well as contextual detail in the room. This worked well in the "pilot phase" consultations. Once remote consultations became "business as usual," it was harder for staff to find time to recruit participants and alert the research team for a planned consultation. This meant that 12 recordings were captured within the clinic but not on the patient end.

For personal/laptop computers, we used a commercially available screen capture software tool to record screen images showing on each party's computer screen as a video file. We used an encrypted USB device to run this software on laptops/computers and positioned a second digital camera for tablets and mobile devices.

Table 1. Overview of cross study sample.

Illness	Total recorded	Male/female	Age range in years, median (SD)	Ethnicity (n)	Technology
Diabetes	18	5/13	21-50 (28)	White British (6); white other (2); black Caribbean (2); Asian Bangladeshi (2); Asian Indian (3); Asian other (3)	Skype using a personal computer (PC), laptop, tablet, or mobile phone device
Cancer	12	4/8	55-84 (74)	White British (8); white other (1); Asian Indian (1); black Caribbean (1)	Skype using PC, laptop, tablet, or mobile phone device
Heart failure	9	4/5	33-87 (76)	White British (9)	Skype or FaceTime using laptop, tablet or mobile phone device

We synchronized screen capture and video files into one using video editing software such that the video of the computer screen can be played exactly in parallel with a video of the patient looking at the screen. We then aligned the patient's and clinician's "ends" in a single editable file. These synchronized files allowed us to zoom in and slow down events to examine interactions, judgments, interpretations [82], the bodily conduct of (patient and clinician) participants, and the ways in which objects (eg, mobile devices and patient records) come to gain significance at particular moments [83]. We have also transcribed consultations using ELAN, a specialized program for transcribing and analyzing video and audio resources that has allowed us to capture verbal and nonverbal details of interactions and view these interactions repeatedly (a requirement of linguistic analysis [56,82]) and annotate audio and video streams at the level of a sentence, word, comment, or any other linguistic feature.

Ethnographic data, in the form of field notes from patients' homes and each of the clinics, provides details of the patient's domestic support, material circumstances, and cultural factors impacting on their self-management as well as the physical circumstances, under which the clinician makes the remote call, including the use of additional technologies (eg, electronic records).

Analysis

Analysis is informed by ethnography of communication and discourse analysis (see above). Our focus is primarily on the (video-recorded) remote consultation data, which will be our starting point for the analysis. We will draw on the (audio-recorded) face-to-face consultation to explore the differences in talk across the 2 genres and on field notes to understand the clinical, organizational, material, and cultural contexts in which both face-to-face and remote consultations take place.

We will initially focus on any differences across all remote consultations, which will include exploring any differences in how the condition being investigated shapes the remote interaction, attending systematically to the contextual factors that may be producing any differences (eg, restricted visual field), the "communicative competence" [76] that participants in remote consultations deploy, and the competencies needed to maximize the benefits of the encounter. We will compare remote and face-to-face consultations to explore whether and how the affordances of the remote medium (ie, the way it constrains and enables interaction) change the interactional structure and content of the consultation and whether the spatial distance between participants, along with the fact that patients are somewhere other than the institutional space of the clinic, often their domestic space, alters the social and power relationships.

We will examine the patterning of interaction in remote consultations at a micro level, how consultations are managed by participants turn by turn and moment by moment using a range of discourse analytic techniques. On the basis of work done so far [18], the issues we think are likely to repay close analysis include the following: opening sequences (which have been shown to work differently in video environments [64,84]),

the management of turn-taking (which may be affected by the way technology constrains participants' visual orientation to each other and to relevant objects [62,85]), the use of back-channeling and other displays of acknowledgment/active listening (verbal and potentially nonverbal, eg, changes in head position [86]), repair (how participants deal with interactional problems, including those whose source is the remote location or the technology itself [87]), the use of questions (including whether/how patients and clinicians use them [88]), and the expression of stance and affect (particularly when clinicians need to communicate complicated or sensitive information or make requests/ask questions that might embarrass a patient).

Project Management and Governance

The QuARC study will be based at the University of Oxford and include NHS partners in participating sites in Oxford and East London. The study is largely desk-based, involving a researcher with specialist experience in linguistics (LMS) bringing together and analyzing existing datasets. Meetings between team members will occur at least monthly by teleconference and 3-monthly face-to-face to share emerging findings and develop the analysis.

The program will be supported by an independently chaired, intersectoral steering group with representation from health services, policy makers, lay members, and external academics. We anticipate that this group will serve as an intersectoral discussion forum, a conduit to national policy, and a link with front-line clinical teams.

Patient and Public Involvement and Engagement

Patients and their caregivers have been key to our research on remote consultations. We set up a dedicated patient advisory group (PAG) in 2015, the main purpose being to incorporate patient feedback within our work. Patients have reviewed key documents and fed back experiences about remote consultation services. Members of PAG felt that all patients should be offered the remote consultation option so that services would be available to all patients who chose it. This view was strongly and universally held. Implicit was the assumption that all patients, and clinicians, are au fait and confident with the technology and are able to manage (potentially very different) ways of communicating online. This insight informed our decision to develop guidance to support patients and clinicians when communicating online (see below).

Ethics

Approval for VOCAL and OTQS studies was gained from National Research Ethics Service Committee London–City Road and Hampstead (REC reference: 14/LO/1883) on 2014 Dec 8 and South Central–Berkshire Research Ethics Committee (15/SC/053), respectively. All participating staff and patients in both studies gave their informed consent to be audio- and video-recorded during consultations and for data to be used for research purposes.

Results

We seek to place detailed, granular descriptions of communication in technology-mediated consultations in the

public domain. We believe that the emerging field of remote consultations will benefit from our research (particularly given the current sparsity of high-quality qualitative studies) and that our methodology may be taken up and applied by others interested in the interactional detail of remote consultations.

Our plan for dissemination is as much about contributions to the process as it is about end outputs [89]. Hence, an important feature of the QuARC study will be the level of collective engagement by different stakeholders in the unfolding project. We already have a network of policy makers (eg, NHS Digital), NHS Trusts (currently over 50), and patient/caregiver groups (eg, Diabetes UK) interested in or already using remote consultations. Drawing on techniques successfully applied in health technology codesign [90,91], we will invite professional, clinical, and service user representatives from across these sites to a series of codesign workshops and use a mix of presentations, video extracts, and interactive tasks (eg, card prompts) combined with narrative-based approaches (eg, “storyboards”) to collaboratively develop draft guidance for clinicians and service users. Guidance will be refined and finalized remotely, producing resources for patients and clinicians that can support effective communication in remote consultations and help to avoid/resolve problems (eg, regarding the technology and how it shapes or constrains clinical aims and outcomes).

Discussion

The QuARC study is intended to deepen our understanding of how remote consultations work (and what makes them work more or less well) and benefit patients and clinicians by offering practical guidance on maximizing the effectiveness of remote consultations and avoiding/resolving any problems associated with mediation, such as transactional problems which may

interfere with the achievement of desired clinical aims and outcomes or interpersonal problems which may affect the clinician-patient relationship. There is already a significant body of research focused on communication and interaction in face-to-face consultations [48,50,52-55]. To our knowledge, this is the first study, in which fine-tuned microanalysis of interactions in remote consultations will be conducted. We will also compare interaction across remote and face-to-face consultations. The latter will necessarily be limited given that our face-to-face comparator data consists of audio-recorded (ie, verbal) and not video-recorded (ie, visual) data. The study deliberately focuses on a small number of consultations undertaken in 3 clinical services in the English NHS. We anticipate rich insights into the communicative utility of the remote genre; however, caution will be needed in considering relevance to other settings and conditions.

One of the key findings of our work on remote consultations to date has been that although some clinicians are very keen to use this format, others are reluctant or opposed. One major benefit of having written, agreed guidance for both patients and clinicians is that the more reluctant clinicians will (we anticipate) be more confident to try this approach themselves. The written guidance could form the basis of local or national short courses and be submitted to Royal Colleges for consideration and endorsement. In this way, we believe that we will support a steady increase the number of clinicians willing to use the new technology and support them to do so safely and appropriately. However, we offer a final note of caution. In our experience, both clinicians and patients come on board gradually. Some are early adopters, whereas others are (for various reasons) more reluctant. What we are hoping for is to “shift the bell curve” through the provision of systematic, evidence-based guidance, thus helping to normalize this new way of interacting.

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Authors' Contributions

SES had the initial idea for the study. DC and SES refined the application for funding to NIHR with input from TG, JW, SV, SB, JM, and CA. In particular, DC and LMS contributed by providing methodological perspectives on the analysis of language and communication, and SV, SB, and CA provided clinical perspectives on diabetes mellitus, cancer, and heart failure, respectively. SES and DC led on writing the protocol with input from all other authors. All authors have checked and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DNA: did not attend

DREAMS: Diabetes, Review, Engagement and Management via Skype

NHS: National Health Service

NIHR: National Institute for Health Research

OTQS: Oxford Telehealth Qualitative Study

PAG: patients advisory group

QuARC: Qualitative Analysis of Remote Consultations

RCT: randomized controlled trial

VOCAL: Virtual Online Consultations-Advantages and Limitations

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Original Paper

The Development of Complex Digital Health Solutions: Formative Evaluation Combining Different Methodologies

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Abstract

Background: The development of digital health solutions for current health care settings requires an understanding of the complexities of the health care system, organizational setting, and stakeholder groups and of the underlying interplay between stakeholders and the technology. The digital health solution was founded on the basis of an information and communication technology platform and point-of-care devices enabling home-based monitoring of disease progression and treatment outcome for patients with rheumatoid arthritis (RA).

Objective: The aim of this paper is to describe and discuss the applicability of an iterative evaluation process in guiding the development of a digital health solution as a technical and organizational entity in three different health care systems.

Methods: The formative evaluation comprised the methodologies of contextual understanding, participatory design, and feasibility studies and included patients, healthcare professionals, and hardware and software developers. In total, the evaluation involved 45 patients and 25 health care professionals at 3 clinical sites in Europe.

Results: The formative evaluation served as ongoing and relevant input to the development process of the digital health solution. Through initial field studies key stakeholder groups were identified and knowledge obtained about the different health care systems, the professional competencies involved in routine RA treatment, the clinics' working procedures, and the use of communication technologies. A theory-based stakeholder evaluation achieved a multifaceted picture of the ideas and assumptions held by stakeholder groups at the three clinical sites, which also represented the diversity of three different language zones and cultures. Experiences and suggestions from the patients and health care professionals were sought through participatory design processes and real-life testing and actively used for adjusting the visual, conceptual, and practical design of the solution. The learnings captured through these activities aided in forming the solution and in developing a common understanding of the overall vision and aim of this solution. During this process, the 3 participating sites learned from each other's feed-back with the ensuing multicultural inspiration. Moreover, these efforts also enabled the consortium to identify a 'tipping point' during a pilot study, revealing serious challenges and a need for further development of the solution. We achieved valuable learning during the evaluation activities, and the remaining challenges have been clarified more extensively than a single-site development would

have discovered. The further obstacles have been defined as has the need to resolve these before designing and conducting a real-life clinical test to assess the outcome from a digital health solution for RA treatment.

Conclusions: A formative evaluation process with ongoing involvement of stakeholder groups from 3 different cultures and countries have helped to inform and influence the development of a novel digital health solution, and provided constructive input and feedback enabling the consortium to control the development process.

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KEYWORDS

eHealth; telemedicine; stakeholder participation; formative evaluation; participatory design; intervention theories

Introduction

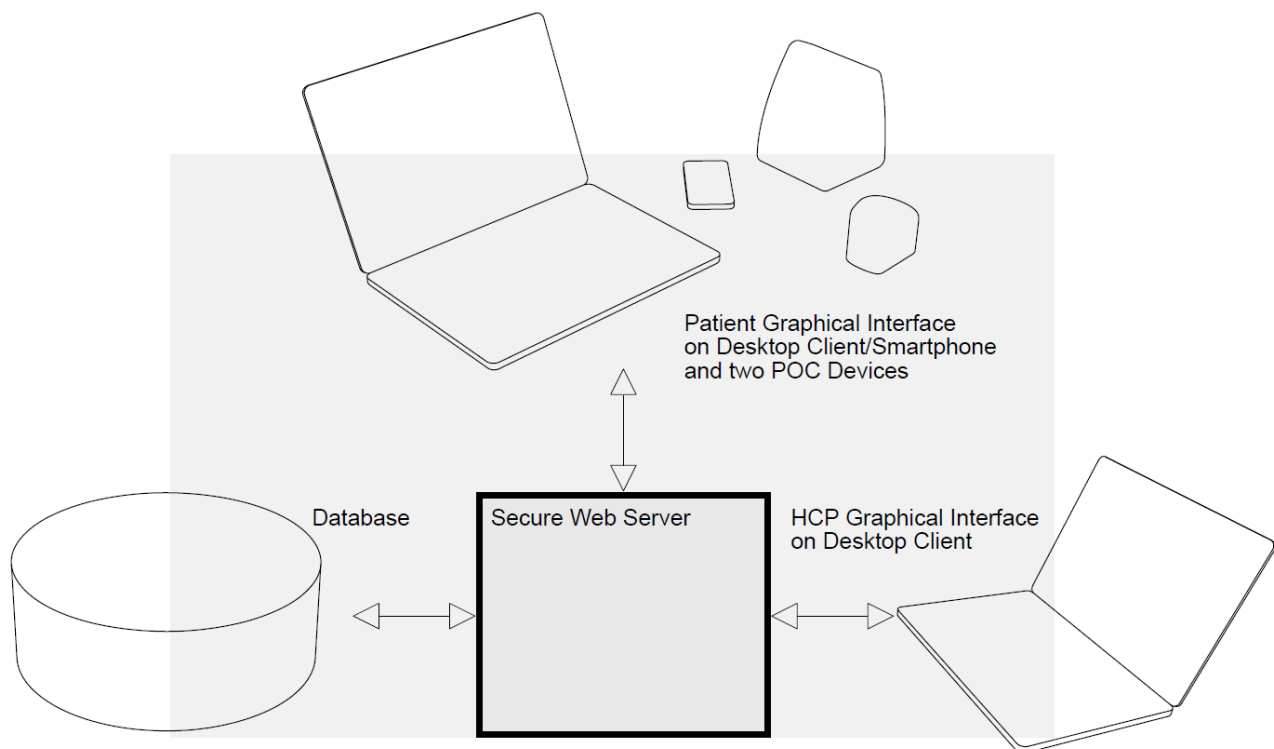
Digital health solutions involve the use of telecommunication and virtual technology to deliver health care outside the traditional health care facilities [1]. The importance of digital health solutions as a vehicle for delivering timely care over distance is on the rise due to increased health needs that have overwhelmed health care sectors across the globe [2]. The widespread use of information and communication technologies (ICTs) in daily life and the growing focus on patient-centered care and self-management strategies have promoted an acceptance of moving health care delivery from the established health care facilities to solutions that come directly into peoples' homes [3-5].

Rheumatoid arthritis (RA) is a chronic, inflammatory disease that leads to joint damage and loss of physical function, and it affects about 3.5 million individuals across Europe [6]. Current clinical care includes assessment of the patient's joints, analysis

of blood samples, and reviewing patient-reported outcomes (PROs). The wide range of treatment options and increasingly specific treatment goals has made the management of RA difficult, and traditional monitoring methods typically involve visits to the hospital that are both time-consuming and resource-intensive.

The Horizon 2020 project eHealth in Rheumatology (ELECTOR) was launched in 2014 with the aim of developing and implementing a digital health solution founded on the basis of an ICT platform for home-based monitoring of disease progression and treatment outcome for patients with RA. The goal of this project was to develop a digital health solution as an alternative to some of the standard visits to the hospital outpatient clinic. The project was a public-private collaboration that included 3 outpatient clinics in the United Kingdom, the Czech Republic, and Denmark and an international team of hardware and software developers, clinicians, designers, and researchers from the Netherlands, the UK, the Czech Republic, and Denmark [7].

Figure 1. The ICT platform enabling open-source data storage and exchange through secure internet access to a web-based graphical user interface for patients and healthcare professionals (HCPs). PoC: point-of-care.



In the ELECTOR project, the concept for home-based monitoring of patients with RA encompasses an ICT platform and point-of-care (PoC) devices as well as new methods of organizing outpatient consultations, as illustrated in [Figure 1](#). The development of the solution was guided by a formative evaluation using a range of methodologies and involving key stakeholders across 3 health care settings in Europe. The aim of this paper was to describe and discuss our experiences from this 2-year evaluation process.

Methods

Study Design

The ICT platform enables open-source data storage and exchange through secure internet access to a web-based graphical user interface for patients and health care professionals. The platform is available on computer, tablet, and smartphone as a “bring your own device” initiative. The ICT platform enables video communication, reporting of PRO data, and connection to PoC devices that can analyze blood samples at the patient’s home.

Several different blood parameters such as high sensitivity C-reactive protein (hsCRP), alanine aminotransferase (ALT), white blood cell (WBC), and hemoglobin (Hgb) are tested to monitor RA and its treatment, and as none of the available PoC devices can perform all these tests, 2 new PoC devices were used. The PoC device for analyzing WBC and Hgb is not yet approved for patient use and thus managed by health care professionals attending the patient at home. The PoC device for analyzing hsCRP and ALT is under development.

With the ICT platform was in place, patients made an assessment of their joints and used the PoC device to analyze blood samples. They also completed several PRO questionnaires and send the data to the hospital. At the outpatient clinic, the health care professionals assessed the data and responded to the patients accordingly via synchrony (video) or asynchrony (mail). Background information and instruction material were required for both patients and health care professionals.

Development of the digital health solution was guided by a formative evaluation engaging a consortium that was established to ensure the development of a solution that would be applicable in all the 3 different health care systems. The consortium included the project coordinator, clinical researchers from the 3 clinical sites, software and hardware developers, and an evaluation team. The outcome of each evaluation activity was shared within the consortium through written reports, oral presentations, and discussions at regular meetings to optimize mutual understanding and insight into the ICT platform and its components.

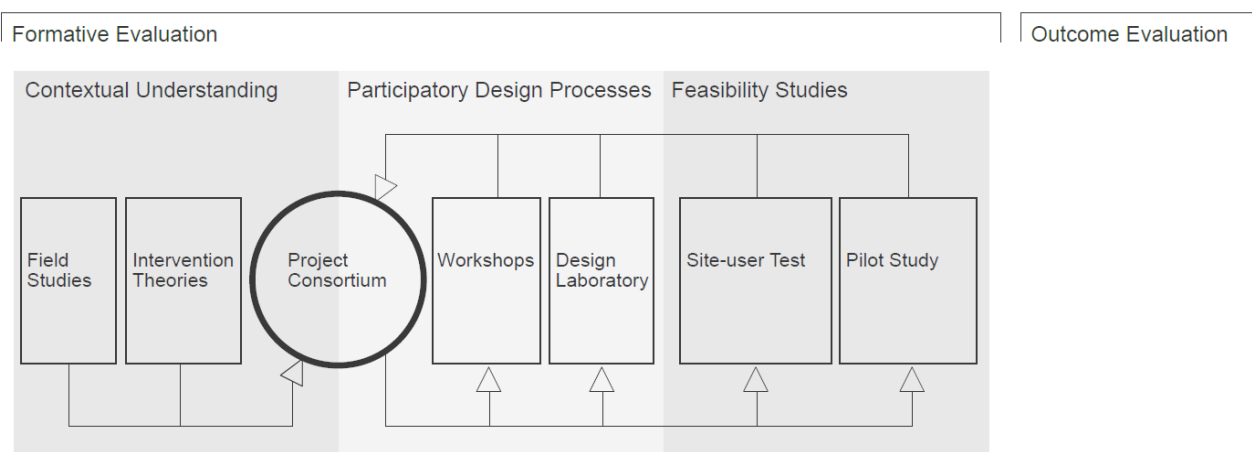
The digital health solution was developed in 3 languages, and variations in culture as well as treatment traditions were to be reflected in the adaptability of a coming solution. Patients, health care professionals, and the local outpatient clinic managers were identified as end users of the technology and thus the key stakeholders to be included in the evaluation. Patients were recruited through affiliated research departments, and we aimed to include a diverse group of patients in terms of sex, age, duration of RA, distance to the outpatient clinic, and socioeconomic status. Health care professionals were recruited from the 3 participating clinics and included both physicians and nurses. A total of 45 patients, 25 health care professionals, and local managers from each of the 3 clinics participated in the evaluation.

The study activities were approved as required by the local health authorities in the participating countries. Study participants received written and oral information about the study and provided written consents.

Evaluation Methodologies and Activities

The formative evaluation included the following 3 primary methodologies: (1) contextual understanding, (2) participatory design processes, and (3) feasibility studies. Each of these contained several activities that were designed along the way as the need for new insights emerged and because the outcome of one activity influenced the subsequent activity. An overview of the primary methodologies and activities is presented in [Figure 2](#).

Figure 2. Methodological approaches and activities used to evaluate the development of the eHealth concept.



Contextual Understanding

Before initiating the development process, we conducted field studies and a theory-based stakeholder evaluation with the overall aim of gaining contextual knowledge about the routine outpatient management of RA and the ideas and assumptions among stakeholder groups.

Field Studies

In March and April 2015, we conducted 2 days of field studies at each of the 3 clinical sites to gather information about the clinical context, identify the stakeholder groups, and engage the clinical sites in the development of the digital health solution.

We observed daily clinical practices and held informal interviews [8] with health care professionals and patients. Field notes were made during the clinic visits and were used to describe the clinical sites, key stakeholder groups, and clinical routines in the outpatient treatment of RA.

Intervention Theories

From April to October 2015, we conducted a theory-based stakeholder evaluation to achieve a multifaceted picture of the ideas and assumptions held by the stakeholder groups. This was a combination of an intervention theory approach and a stakeholder approach aimed at improving evaluation practice and intervention quality when various stakeholders are assumed to be decisive for the implementation and functioning of an intervention. Intervention theories are defined as presuppositions of how an intervention may impact a given situation by changing or preserving it in ways that are preferable or not preferable to a situation without the intervention or with another intervention [9].

Initially, we developed the common intervention theory or the so-called “principle of reason” for the concept. This was based on project descriptions, presentations of the digital health solution, written material describing the current clinical care, and discussions within the project consortium. Next, we developed intervention theories for each key stakeholder group. From August to October 2015, we held group and individual interviews with a total of 16 patients and 22 health care professionals at the 3 clinics (Table 1).

A semistructured interview guide was used, and a prototype of a PoC device served as a prompt during interviews. The interviews were audiotaped and transcribed, and the transcripts were categorized into the following predetermined themes: (1) situation theory (interpretations of present challenges), (2) normative theory (perceptions of the preferred or ideal situation), and (3) causal theory (assumptions of how the intervention works). A description of each theme was then formulated for each stakeholder group and presented in a matrix comparing the principle of reason theory with the intervention theories of the patients and health care professionals at each clinical site. This allowed the similarities, differences, and possible conflicts between stakeholder groups to become apparent (Multimedia Appendix 1).

Participatory Design Processes

The aim of the participatory design approach was to develop the technical systems and the related organization in close cooperation with end users early in the design and development process and in a contextualized and realistic setting [10-12]. The participatory design process included workshops at each of the 3 clinical sites as well as a design laboratory facility established at the Copenhagen site.

Workshops

One workshop was held at each of the clinical sites between August and October 2015. The aims of the workshops were to gain knowledge about the overall usability of the graphical user interface and PoC devices and to gain knowledge about patients' and health care professionals' perceptions of the digital health solution. In total, 10 patients and 18 health care professionals participated in the workshops (Table 1). Each workshop included “hands-on” sessions and “think aloud” methods [13] in small groups of patients and health care professionals, as well as discussions of the advantages and disadvantages of the solution in groups of patients and health care professionals and in plenary.

Hands-on sessions included the following steps: (1) patients conducting a monitoring session while the health care professionals observed, that is, logging on to the system, completing the PRO questionnaires, and filling in the (predesigned) blood test results, (2) health care professionals logging on to the system and receiving data while the patients observed, (3) patients and health care professionals conducting a virtual consultation. During the sessions, the patients and health care professionals were encouraged to comment on what they experienced (think aloud) and share their thoughts afterward.

Following the hands-on sessions, the groups of patients and health care professionals discussed perceived strengths and possibilities and weakness and challenges of the solution. These discussions were audiotaped and transcribed. Transcriptions and notes taken during the sessions were compiled as text, photos, and drawings.

Design Laboratory Facility

The design laboratory was established in 2015 as a “home-like setup” in an apartment at the Copenhagen clinic. Its aim was to help developers to answer specific questions such as “Does this device or process work and how can it be refined?”

In a series of short sessions, prototypes of PoC devices, lancets for drawing blood, and cartridges for blood sampling were tested through a dialogue between the patient and designer while iteratively sketching and evaluating prototypes and different scenarios for blood testing (Table 1). These sessions were observed by developers and a researcher taking notes and photos and interviewing patients.

Table 1. Evaluation activities performed between 2015 and 2017.

Activity	Aim	Place and participants	Data collection	Outcomes
Field studies, Primo 2015	Gaining knowledge of contexts and daily practice, creating collaboration, and identifying key stakeholders.	Outpatient clinic at the 3 clinical sites. Actors involved in the work at the clinics.	Observations and informal interviews with health care professionals and clinic management.	Descriptions of daily clinical practices as input for identifying stakeholders and further evaluation.
Intervention theories, Medio 2015	Developing intervention theories for key stakeholder groups.	At the 3 clinical sites. 16 patients (aged 25-75 years, 11 females) and 22 health care professionals (16 females), including 3 clinic managers.	Semistructured interviews (individual and group).	Descriptions and comparisons of intervention theories across stakeholder groups. Report served as input to the ongoing development of the digital health solution.
Workshops, Medio 2015	Insights into patient and health care professionals' perceptions of the digital health solution and overall usability of the graphical user interface.	At the 3 clinical sites. 10 patients (aged 26-69 years, 6 females) and 18 health care professionals (13 females).	"Hands-on" sessions and "think aloud" exercises in small groups of patients and health care professionals. Group and plenary discussions of pros and cons of the digital health solution.	Presence of developers enabled immediate adaptations. Reports served as input to the technical and the organizational development as well as the clinical value creation.
Design laboratory, Ultimo 2015	Testing how patients handled different lancets and cartridges for blood sampling.	At the design laboratory. 2 patients (1 female).	Patients drew a drop of blood and filled a cartridge. Sessions included observation, dialogue, drawing, and generation of ideas.	Recommendations and optimizations in a fast turnover. Provided valuable input to the design and development of point-of-care devices and related test cartridges.
Site user tests, Primo 2016	Testing the "lifecycle management" of the technology.	At the 3 clinical sites and the patient's home. 15 patients (aged 25-83 years, 9 females) and 3 health care professionals (3 females).	Home monitoring for 1 week. Log data from the information and communication technology (ICT) platform, notes from health care professionals, diary, and photos from patients.	Descriptive analysis reported for each site, resulting in revisions of the technical and organizational setup of the digital health solution and the related briefing and communication material.
Design laboratory, Medio 2016	Test of different scenarios for blood testing.	At the design laboratory. 4 patients (3 females).	Following a short introduction, patients performed a blood test. Sessions included observation, dialogue, drawing and generation of ideas, and interviews.	Descriptive analysis reported. Served as input to the organizational development.
Pilot study, Ultimo 2016	To test real-life functionality of the digital health solution.	At the clinical site in Copenhagen and the patient's home. 5 patients (aged 55-83 years, 4 females) and 1 health care professional (female).	Home monitoring for 3 weeks. Log data from the ICT platform, notes from health care professionals, diaries, and photos from patients. Subsequently, interviews with the 5 participating patients.	Interim analysis reported. Indicated a "tipping point" and a need for further development.

Feasibility Studies

The feasibility studies included a site user test at each clinical site and a pilot study at the Copenhagen site. These were completed during 2016. The feasibility studies were used to test if an intervention could be performed in a particular setting and to investigate how contextual factors influenced the implementation of the technology. The aim was to provide feedback to the developers to create learning and a basis for adapting the technology to its actual users and the implementation context [14].

Site User Tests

The aim of the 1-week site user test was to assess the "life cycle management" of the concept, that is, the practical aspects of handing out, taking home, and installing the ICT platform components. At the clinic, the patients received oral instructions on how to perform joint assessment, how to connect to the ICT platform, and how to communicate with the clinic. The prototypes of PoC devices, written information, a Polaroid camera, and a notebook were then handed out to the patients. At home, patients connected to the ICT platform from their own computer using a secure log-in. Every second day, they completed a joint assessment and the PRO questionnaires and entered the results of the blood tests and also

video-communicated with the health care professionals at the hospital. A total of 15 patients and 3 health care professionals participated in the site user tests (Table 1).

Data collected from the site user tests included log data from the ICT platform and health care professionals' notes during the test. Patients' experiences were collected via a cultural probe [15] consisting of a notebook, a Polaroid camera, and a leaflet explaining the intended use for capturing patients' experiences with the digital health solution. Based on these data, descriptive analyses were made focusing on the patients' and health care professionals' attitudes toward the home monitoring concept and experiences with the solution, including technical and organizational issues as well as issues related to task performance.

Pilot Study

The pilot study was planned as a 3-week pilot study with 30 patients and was conducted at the clinical site in Copenhagen from December 2016 to January 2017. The aim of the pilot study was to test the "real-life organizational setup" of the concept, and it served as a base for a subsequent outcome evaluation (Table 1).

After getting instructions at the hospital, patients brought home the leaflet outlining the intended use along with the 2 PoC devices, which were then connected to the ICT platform from their own PC using a secure log-in. Every second day, they performed home monitoring, including joint assessment, PRO questionnaires, blood testing (predefined results were used), and virtual contact with the hospital.

Data included compliance with scheduled activities, use of a hospital hotline for technical and health-related inquiries, and experiences of patients and health care professionals retrieved through notes, diaries, photos, and patient interviews.

Results

Contextual Understanding

The initial field studies enabled us to identify key stakeholder groups and provided us with knowledge about the different health care systems, professional competencies involved in routine RA management, clinics' working procedures, and use of communication technologies. For example, while RA management in Denmark is hospital-based and patients can choose to have blood tests at hospital or the general practitioner's clinic, RA management in England is collaboration between hospitals providing RA consultations and general practitioners responsible for undertaking blood tests and prescribing medications. In CZ, RA treatment is primarily located in a single, central hospital that presents extended travel distances for patients.

The intervention theories added valuable insights into stakeholders' perceptions of challenges in routine outpatient treatment, their ideals for an enhanced clinical practice, and their assumptions about the impact of the digital health solution. Although the comparative analysis of intervention theories did not indicate irreconcilable conflicts across stakeholder groups at the 3 sites, it did reveal differences in stakeholder groups'

assumptions about the concept. The patients were generally very enthusiastic and envisioned greater flexibility with fewer consultations at the clinic, thus avoiding time taken to travel and to book and undergo regular blood tests. The health care professionals saw not only great advantages for patients but also challenges in relation to resources needed for implementing new practices in an already busy schedule, uncertainty as to which patient the concept would be the most relevant to, and how home monitoring would impact the patient population seen at the clinic. While physicians anticipated advantages from the extra clinical data collected, nurses anticipated additional tasks in assessing blood tests and PRO data. This was especially the case in UK, where PRO data are not routine and blood tests are usually assessed by the general practitioner. The nurses in CZ hoped for greater responsibility in assessing patient data, which is presently undertaken by physicians. Clinic managers could see financial, legal, and organizational challenges; however, they could also see the possibility of fewer face-to-face consultations, easing the limited physical capacity at the outpatient clinics.

The principle of reason of the concept was discussed in the consortium, enabling a common understanding of how the concept might be developed and implemented across the 3 countries. The results from the intervention theories also served as input to the design of the future outcome evaluation.

This contextual understanding informed the participatory design processes as well as the initial considerations for the organization and implementation of the solution. Finally, we found that field visits to the 3 clinical sites were of great value to the collaborative processes in the project. The value of interactive development of the design was acknowledged individually by all 3 countries, where both participating patients and health care professionals acquired inspiration from the presentation of considerations and solutions obtained at the other sites.

Participatory Design Processes

During the workshops, patients and health care professionals gave feedback on the user interface and PoC devices. Patients had several ideas for improving the platform's procedural flow, the joint assessment tool, and the PRO questionnaires. They also commented on the terminology used and stressed the importance of applying commonly used terms rather than technical terms and abbreviations. This feedback was essential to the further refinement of the user interface. The group and plenary discussions that followed these think aloud sessions gave us insights into patients' and health care professionals' immediate views on the platform and devices and on the digital health solution as a whole. The inclusion of both patients and health care professionals in the workshops was extremely useful, as this revealed the different perspectives of the 2 stakeholder groups and enriched the workshop discussions.

The laboratory facility allowed a short development turnover time for specific parts of the technologies involved. Patients were presented with visual mock-ups and working prototypes, and they provided valuable input in cooperation with a product designer. The information provided was used to create new prototypes and to fine-tune working scenarios. After testing

several lancets available on the market for drawing blood, one was deemed appropriate for persons with reduced dexterity.

Initially, 2 PoC devices for analyzing blood samples were chosen for inclusion in the project. As neither device was at the time approved for patient self-testing at home, it was decided to test the cartridges used for blood sampling. The cartridge of one of the initially tested PoC devices was still under development and was changed on the basis of the feedback from patients. The cartridge of the other PoC device was found to be inappropriate for self-testing, and the device was thus replaced by 2 PoC devices, which further increased the complexity of the home-testing. As a result, we compared home-testing versus kiosk-testing (patients taking blood samples in a local setting, eg, general practitioners' office or pharmacy, with health care professionals at hand), and the subsequent interviews with the patients led us to further considerations about how to organize the eHealth blood testing and indicated the need for more information and instructions. The patients and health care professionals testing the various devices gave valuable and necessary feedback to the developers of the equipment, which in the end saved the companies from futile investments in nonoperational processes.

Feasibility Studies

The site user tests provided us with valuable understanding about the time needed for patient instruction prior to home monitoring and the handling of equipment and supplementary materials to take home. The tests also gave us insight into the types of challenges patients met when connecting to the ICT platform from home and performing the tasks allocated for the week.

Recording the extent and content of hospital help requested by patients helped us in the subsequent establishment of patient call centers. Log data provided information about patient compliance and how they completed the tasks allocated for the week. The majority of patients completed the tasks. Some patients had difficulties connecting to the ICT platform the first time, and others got confused by the short message service (SMS) text messages reminding each of the several tasks to be fulfilled on the same day. Despite commenting on the amount of time needed for examining, answering questions, and doing blood tests, patients were still in favor of testing at home and anticipated a possibility of recording RA-related problems in real time as an alternative to recounting them at the time of fixed visits to the clinic.

The comments made by patients in the notebook and illustrated by photos were extensive and very useful. Patients described their thoughts and experiences, for example, making room for the equipment at a desk and in the fridge, finding enough electric sockets, needing the help of a son and alike. One patient drew illustrations showing ideas for easy packaging and storage.

A report was produced for each site that described the lessons learned from the hospital and home environments. These reports were shared within the consortium and resulted in adjustments being made to resolve the reported issues before pilot testing.

Due to a need for testing changes and developments since the site user tests and to ensure time for further developments ahead

of a clinical test scheduled for 2017, a pilot test was initiated in December 2016. Acknowledging the technical changes taking place right up to the start of the pilot study and the limited number of PoC devices available, it was decided to test in a series of 5 patients at a time. However, after the first 5 patients had completed the 3-week test, it was decided to discontinue the pilot study due to several technical challenges: (1) unstable internet connection, (2) missing SMS text messages to patients prior to tasks to be performed, (3) missing status updates and warnings to health care professionals when patients did not fulfill tasks, (4) failed connectivity between the PoC device and the ICT platform, (5) mechanical breakdown of one PoC device, and (6) final information material being too complex due to complicated PoC device instruction manuals.

These challenges resulted in patients not being able to connect to the ICT platform at various time points and video connections being unstable and of poor quality. The result was a disproportionate amount of resources used by patients calling the hotlines and the health care professionals trying to fix the technical challenges. The missing SMS text messages and status updates meant that some activities were not completed, and the comprehensive information material only seemed to add to the complexity of activities that patients were asked to perform. Despite this, at the subsequent interviews, the patients were still in favor of the digital health solution but pointed to a need for further development, the message being to make it simple and self-evident.

The feasibility study provided decisive insights into real-life use of the technology, including fundamental and necessary information about challenges and pitfalls in relation to the ICT platform and PoC devices and the information and instructions needed and how best to organize the workflow of the technology. Following an interim report after the first 5 patients had completed the pilot testing, a time-out was decided and a series of meetings and workshops were initiated within the consortium aimed at supporting and consolidating further development prior to the planned outcome evaluation.

Discussion

Principal Findings

The aim of the ELECTOR project was to develop and test a digital health solution for home-based monitoring of RA, including an ICT platform and supplementary components, across 3 different health care systems. Ongoing and systematic evaluation is important in the development of digital health solutions [16]. Evaluations of complex interventions need to be comprehensive and should include theoretical understanding and development work to ensure mutual learning [14,17]. Descriptions of the development process and the impact of ongoing evaluation also help to interpret the results of the intervention at a later stage [18]. The development process is ideally described as a chain of reasoning that leads from a statement of a problem to the definition of a solution and includes the following 7 steps of identification: drivers, visions, goal, objectives, requirements, design, and solution [16].

The vision of the ELECTOR project was to develop a more individualized treatment schedule that would reduce resource-demanding visits to the hospital for patients with RA with low disease activity, and this vision was developed and described during the funding application process [19]. The solution was conceptualized as a digital health solution including different components that were either under development or already developed but needed adjustment before use by patients with RA at home. Although the evaluation was in accordance with the steps recommended [16], a full requirement development process was not possible because the development of the solution and its components was already well advanced. Moreover, because the overall framework for creating this digital health solution was based on combining products and solutions from various companies and embedding them in a range of very different clinical settings, the formative evaluation thus served as an ongoing input that enabled learning as well as adaptation of the technical, clinical, visual, and organizational aspects of the concept.

The development of a technology that can accommodate daily practices of disease management across different settings requires an understanding of the complexity of the health care systems, organizational settings, and stakeholder groups involved as well as of the interplay between these and the technology in question [20,21]. The inclusion of 3 hospital sites representing different health care systems made it clear that the visualized solution can present different challenges in different health care systems, for example, in terms of responsibilities and competences of patients and health care professionals and the daily routines and collaborations. The use of field studies and intervention theories helped us to identify local visions and requirements related to the general implementation of the solution as well as those that were specific to the individual sites.

Numerous studies point to a multiplicity of barriers related to the implementation of digital initiatives among stakeholder groups [22,23]. The involvement of key stakeholders and real-life experiences is thus crucial. With the aim of developing a solution that would be relevant and would give added value to everyday practice, we established a consortium of stakeholders to ensure ongoing feedback to guide the development process. This input and feedback contributed to a wide range of adjustments in technical, visual, and practical components as well as adaptations in the conceptual design and organization of the digital health solution.

The learnings captured through these activities supported the development of the digital health solution and aided in identifying a “tipping point” [24] during a pilot study. Patients, health care professionals, and managers confirmed the relevance and value of the overall concept as well as the organizational setup. However, due to a range of challenges related to the

technical components of the ICT platform, the pilot study came to a hold, allowing further development of the ICT platform and its components. Hence, the ongoing involvement of stakeholders and feedback to the consortium throughout the development process safeguarded us from initiating a large multicenter test at a time when the technology was in fact not ready.

Strengths and Limitations

Although the evaluation was instrumental for the development of the digital health solution, it has some limitations. The project included several national clusters in differing clinical settings and related industries, and thus, the stakeholders were located in different countries and were not readily available. Due to the travel distances, the evaluation team was present only a few days at a time at the hospital clinics, and arranging interviews with busy patients and health care professionals was “the art of the possible.” As a result, interviews were performed both individually and in small groups. Furthermore, the laboratory facility was situated at a single location and involved a small number of patients from a specific treatment context.

The learning implied multinational and multicultural feedback, which was essential for the development of a fully operational set of tools for international use, including all aspects of a system for home-based monitoring of arthritis. Though limited by the inclusion of a relatively few patients and health care professionals, the site user tests were valuable by the diversity of the participating centers and gave insight into the technology’s implementation in routine clinical practice in several relevant hospital departments over the 3 countries representing much of the European health care traditions.

Conclusions

This case study clearly demonstrated the advantages of conducting a formative evaluation early in the process to guide the development of a digital health solution. The formative evaluation was designed to inform the development process of a solution that aimed to be applicable and add value to everyday practice for patients and health care professionals in the treatment of RA in different European health care systems. Through a series of formative evaluation initiatives, an iterative process was implemented that included elucidating the inherent intervention theories of the digital health solution and of the patients, health care professionals, and managers and involving users in the design, testing, and adjustment of the solutions of the ICT platform and related components. The ongoing involvement of a range of relevant stakeholders helped to inform and influence the development of the solution. This process provided a basis for sequential formative testing and outcome evaluation and revealed its value in terms of providing constructive input and feedback, enabling the consortium to control the development process of a novel digital health solution.

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Authors' Contributions

HG, PCT, and HB were lead in designing and writing the original proposal for obtaining the funding. JZ and AL were also involved in the original proposal. AL, M Sandvei, M Skougaard, HCA, JM, JZ, and HG conducted the research. M Skougaard, JM, and JZ were responsible for the recruitment procedure. AL was responsible for drafting the manuscript; all authors have contributed to the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

An example of a matrix comparing the embedded intervention theory ("Principle of Reason") of the eHealth project with intervention theories of patients with rheumatoid arthritis (RA) and healthcare professionals at one of the three sites.

[[PNG File, 135KB - resprot_v7i7e165_app1.PNG](#)]

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Abbreviations

ALT: alanine aminotransferase
Hgb: hemoglobin
hsCRP: high sensitivity C-reactive protein
ICTs: information and communication technologies
PoC: point-of-care
PROs: patient-reported outcomes
RA: rheumatoid arthritis
SMS: short message service
WBC: white blood cell

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Protocol

Identifying Barriers and Facilitators of 13 mHealth Projects in North America and Africa: Protocol for a 5-Year Implementation Science Study

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Abstract

Background: Although many mHealth interventions have shown efficacy in research, few have been effectively implemented and sustained in real-world health system settings. Despite this programmatic gap, there is limited conclusive evidence identifying the factors that affect the implementation and successful integration of mHealth into a health system.

Objective: The aim of this study is to examine the individual, organizational, and external level factors associated with the effective implementation of WelTel, an mHealth intervention designed to support outpatient medication adherence and engagement in care in Africa and North America.

Methods: We will adopt the Consolidated Framework for Implementation Research (CFIR) constructs for evaluation of mHealth implementation including a scoring and monitoring system. We will apply the adapted tool to identify facilitators and barriers to implementation of the WelTel mHealth intervention in order to determine how the technology platform is perceived, diffused, adapted, and used by different mHealth project teams and health system actors in Africa and North America. We will use a mixed-methods approach to quantitatively test whether the factors identified in the CFIR framework are associated with the successful uptake of the mHealth intervention toward implementation goals. We will triangulate these data through interviews and focus group discussion with project stakeholders, exploring factors associated with successful implementation and sustainment of these interventions.

Results: The development of the customized CFIR is finalized and currently is in pilot testing. The initial results of the use of the tool in those 13 implementations will be available in 2019. Continuous conference and peer-reviewed publications will be published in the coming years.

Conclusions: The results of this study will provide an in-depth understanding of individual, organizational, and external level factors that influence the successful implementation of mHealth in different health systems and geographic contexts over time. Via the tool's unique scoring system connected to qualitative descriptors, these data will inform the most critical implementation targets and contribute to the tailoring of strategies that will assist the health system in overcoming barriers to implementation, and ultimately, improve treatment adherence and engagement in care.

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KEYWORDS

mobile health; mHealth; text messaging; digital health; implementation science; Africa; North America

Introduction

Background

Billions of dollars are globally spent on health research projects each year, but only a limited number of effective interventions are translated into practice and policy [1,2]. Technology is providing unprecedented opportunities to improve patient engagement in care for better adherence leading to reduced morbidity and mortality, yet a significant knowledge-action gap remains [2]. Many evidence-based innovations are not adequately scaled up to meet the full challenges of the United Nations' global Sustainable Development Goals [1,3-5]. Mobile health (mHealth) is an emerging area of disease management that can help patients adhere to prolonged treatment regimens and improve their quality of care—an area where improvement can have more impact than even discovery of new treatments. Globally, mobile phones are now the most pervasive and accessible form of two-way communication technology. In 2014, the number of mobile phone subscriptions surpassed the number of people, and uptake in vulnerable and marginalized groups has, in many cases, bridged the socioeconomic “digital divide” [6]. Text messaging via short message service (SMS) remains one of the most popular forms of mobile communication and has become the most used data transfer system in the world, with over 24 billion text messages sent and received each day. A landmark randomized controlled trial (RCT), WelTel Kenya1, was the first comprehensive RCT to test effects of text message reminders in improving HIV therapy adherence. The authors showed that bi-directional, weekly text messaging significantly improved adherence to antiretroviral therapy (ART) and increased the proportion of patients with a suppressed HIV viral load in an HIV-positive Kenyan population initiating ART, over a 1-year period [7]. As noted by a recent Cochrane review, this RCT study (and many others) have built a strong body of high-quality evidence supporting the use of weekly text messaging to enhance ART adherence and viral suppression, in comparison to current standards of HIV/AIDS care [8].

Since the original RCT, the WelTel mHealth program has expanded in Africa and North America in the area of HIV/AIDS [9-12], tuberculosis (TB) [13], maternal and child care, asthma, and recently in primary care settings. The WelTel program is a patient-centered form of digital outreach communications designed to support engagement in care and treatment adherence. Using a weekly check-in model, usually via text message, patients self-identify concerns that are then triaged by a point person and connected for care to appropriate health care providers on an “as-needs” basis, leading to a form of patient-centered precision care. With its leading evidence base in HIV and TB, the WelTel program is ideal for an implementation science evaluation as it is in the process of being scaled-up in numerous settings.

Case studies, RCTs, and other quasi-experimental methods generate critically important evidence to determine the efficacy

of an intervention. These methods, however, do not provide the necessary information required to implement comprehensive public health interventions in real-life settings. Implementation science can help fill this gap by studying the process of developing, introducing, institutionalizing, and sustaining policies, programs, and activities in complex settings. This is done by identifying the individual, population, health system, and health environment factors associated with the successful uptake of effective interventions [5,14-18].

Undertaking a comprehensive implementation science study is particularly important when studying mHealth interventions, as the health care system itself is complex, includes multiple interacting components, and interventions must be adapted to fit the needs of a practice setting and patients with different views and expectations [19,20]. However, to our knowledge there is no tested tool that can be continuously used to evaluate, monitor, and inform mHealth implementation processes as they unfold.

Aim

The overarching aim of our 5-year research project is to create and test an implementation research tool that can be used to generate continuous, context-specific evidence that can inform mHealth for impact at scale. To do so, we will evaluate the scale-up process of the WelTel text-messaging mHealth system in different global implementation settings. We will use rigorous scientific methods to assess processes and outcomes with the following main objectives:

1. To adapt the Consolidated Framework for Implementation Research (CFIR) constructs for evaluation of mHealth implementation including a scoring and monitoring system
2. To apply the adapted tool to identify facilitators and barriers to implementation within each program to continuously inform the implementation process
3. To use a scoring framework to correlate implementation factors with measures of implementation success (rate and scale of adoption plus sustainability) across the multiple projects over time

Conceptual Framework

This comprehensive mHealth implementation science study will use the widely cited and used CFIR [5]. The CFIR is an implementation science framework that provides a comprehensive taxonomy of operationally defined constructs from multiple disciplinary domains (eg, psychology, sociology, organizational change) that are likely to influence implementation of complex programs. CFIR constructs are organized into five major domains: (1) characteristics of the intervention (eg, evidence strength and quality, complexity), (2) the outer setting (eg, patient needs and resources), (3) inner setting (eg, compatibility of the mHealth intervention with existing engagement programs, leadership engagement), (4) characteristics of individuals involved (eg, knowledge and

attitudes), and (5) the process used to implement the program (eg, quality and extent of planning, engagement of key stakeholders) [5]. We are using this framework with the primary aim of understanding how the WelTel mHealth program is perceived, diffused, adapted, and used by different mHealth project teams and health system actors in Africa and North America. The CFIR framework draws together the unique and common elements of 19 different theories and frameworks and offers a common taxonomy for exploring the effectiveness of implementation within a specific context [5]. While theoretical frameworks in implementation studies are underused [21], the use of theory in implementation studies can help identify factors that predict the likelihood of implementation success and help develop better strategies to achieve more successful implementation, thus strengthening the understanding and explanation of how and why implementation succeeds or fails (eg, what works, for whom, under what circumstances, and why) [22]. Theories, frameworks, and models can help identify appropriate outcomes, measures, and variables of interest for implementation studies. Theory can also help organize studies when collecting, analyzing, interpreting, explaining, and presenting data [23].

In preparation for this study, the appropriateness of several theories and frameworks were assessed. Several implementation frameworks and theories that exist were considered relevant, such as the Reach Effectiveness Adoption Implementation Maintenance framework [24], the Promoting Action on Research Implementation in Health Services framework [25], the Technology Acceptance Model [21], and the Normalization Process Theory [22]. The CFIR was chosen based on its comprehensiveness and ability to manage both breadth and depth of data given the complexity of mHealth programs. It includes a broad number of aspects related to implementation and is thus considered a helpful framework for identifying barriers and facilitators influencing mHealth implementation. It addresses the need to assess and maximize the effectiveness of implementation within a specific context and to promote dissemination to other contexts.

Since its inception, CFIR has largely been used to help understand the interplay between context and the implementation process. This framework can therefore be adapted and used to guide the design of mHealth interventions for particular settings, as well as the study of their implementation. An increasing number of implementation studies have used CFIR, some as an evaluation framework [23,26,27], some for detecting factors influencing implementation [28,29], and some for classifying these influencing factors as facilitators or barriers [19,26]. To date, only a few studies have employed the CFIR for evaluation of specific technological interventions [19,30,31]. We found only two other studies that used the CFIR developers' method to identify and compare distinguishing constructs between high versus low implementation settings [19,32]. We were unable to find any studies that compared implementation factors in high- and low-resource settings. Finally, we did not find any studies that considered the dynamic nature of implementation by examining barriers and facilitators over time. [33-36]. There is a need for research that assesses, tests, and further develops CFIR's applicability in determining which factors influence

implementation success in the field of mHealth interventions. We will tailor the CFIR for use with mHealth interventions in different settings and contexts.

Intervention Details

The WelTel innovation is an evidence-based, low-cost, easy-to-use, and accessible mobile phone based health communication solution to address the global challenge of inadequate outpatient engagement across multiple diseases. Developed with direct input from patients and caregivers in Kenya, the original WelTel model for HIV care was a weekly two-way text-message check-in by clinic staff to patients using basic mobile phones. Clinicians called patients if they reported a problem via text message, triaged those problems, and provided advice on how to manage them (eg, a care path). This method was first validated in the landmark RCT, WelTel Kenya1, which demonstrated improved patient adherence to HIV treatments and achieving viral suppression, a key target of the World Health Organization (WHO) and the Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 target [7]. The mobile communication model was intended to provide patients with extra support between clinic visits, while maintaining maximal reach and privacy protection through its simplicity and lack of outgoing health-related content. It also extends the capacity of health care providers to look after patients by proactively managing outpatient problems and identifying individuals who require the most support (only 3% of patients identified "problems" each week). Multiple studies have since validated elements of the intervention, such as preferred message frequency (weekly better than daily) and the two-way nature of communication (versus one-way) [37]. The WelTel innovation, and evidence surrounding it, has directly informed global treatment guidelines such as the 2013 WHO ART guidelines and the 2014 International Association of Providers of AIDS Care guidelines for retention in HIV care. Regardless of its effectiveness, there are also different user and technological level challenges in different contexts. The WelTel service has been adapted for TB; maternal, neonatal, and child health; and asthma programs, with interest and the potential to expand to other health conditions in the future (eg, cancer care, primary care). In our adoption of WelTel for TB in British Columbia, Canada, we found that WelTel weekly two-way text messaging did not improve latent TB infection (LTBI) completion rates compared to standard LTBI care. However, completion rates were high in both treatment arms [38]. In a recent RCT to determine whether a text-messaging intervention improved retention during the first year of HIV care, WelTel's weekly text-messaging service did not improve retention of people in early HIV care [39]. With all this mixed evidence and effectiveness across different implementations, we are proposing a continuous 5-year implementation science research on this intervention to identify what works and what does not.

Methods

Overview

In this cross-project, mixed-methods study, we will take an investigative approach to determining what works, what does not, and the specific barriers and facilitators to implementing

the WelTel mHealth service at various programmatic stages. Using a standardized adapted CFIR tool, 13 initial projects will be evaluated at their current state and followed over time at 6-month intervals for up to 5 years. In addition to the adapted CFIR domain narratives, each domain will be scored using a standardized scoring technique (see below) and compared both across projects and longitudinally within projects. The scoring will be used to identify domains and elements within the domains that appear to be doing well (scored highly) or doing poorly (low scores), and how they are associated with successful progress in the implementation of the projects. These factors will then be discriminated in a way that can actively inform individual projects along the implementation process and ultimately lead to an optimized and cost-effective mHealth strengthening opportunity for these health services globally. The evidence from data collection every 6 months will be iteratively analyzed and used as an input to inform the implementation process. The results of each project will be shared with the respective project leaders and discussed in the bi-annual meetings of the research team on the modality of incorporating the evidence into the implementation process. Continuous support will be provided by the research team to see the level of incorporation of the research results into the implementation. Experience sharing visits will be also organized among different projects to facilitate evidence use among all 13 projects.

A novel feature of this study will be a cross-project implementation science evaluation using the CFIR framework. An international consortium for implementation science recognized the need to not only evaluate study endpoints but also conduct formative evaluations to assess the extent to which implementation is effective in a specific context to optimize an intervention’s benefits, improve sustainability, and promote dissemination of findings into other settings. The framework not only evaluates static components of implementation factors that facilitate or impede implementation success but also evaluates processes over time. The CFIR framework is flexible and was designed to be adaptable to a program’s specific needs. For our purposes, we will create a standardized scoring framework and narrative based on the most salient individual constructs of the framework for mHealth research and our specific intervention. This allows us to compare implementation factors across our individual studies in a standardized way and also evaluate them dynamically over time [40].

Data Collection

Members of the mHealth research team will conduct one-on-one interviews or focus groups (depending on availability and

preference of participants) using a purposive sampling strategy that focuses on individuals who are involved in the planning, implementation, or follow-up of their respective mHealth studies. Participants will consist of individual project relevant/representative stakeholders representing the range of stakeholders and representing the five domains. Five people from each project will be included in the qualitative study. To avoid bias, participants will be selected by each project leader rather than the central WelTel team. They will be asked to provide written informed consent. Interviews will be conducted at locations that are convenient for the key stakeholders and will ensure their privacy and confidentiality. Participants will have the opportunity to discuss potential strategies about how their respective project(s) could be improved or strengthened, the influence of internal and external social relationships and climate on the study and acceptance of the intervention, and suggestions for the WelTel mHealth intervention itself. Engaging with these team members through interviews or small focus groups will provide important insights that can guide implementation of the WelTel mHealth intervention in specific contexts. As each project team is at a different phase of their project, we will investigate difference stages of project development, implementation, and follow-up. Data will be collected every 6 months from each of the projects for 5 years.

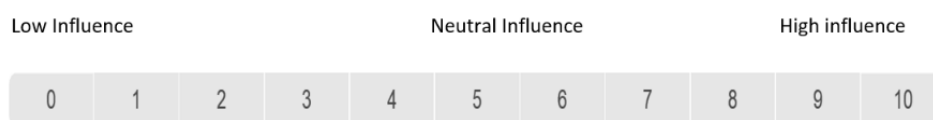
Scoring

Each of the constructs in the modified CFIR will have scoring out of 10. Each of the participants will score each of the constructs, and the median will be automatically calculated. A 10-point scoring approach will be used to flexibly capture the opinion of the study participants. A unique scoring guide will be used to maintain consistency among individual assessments and for standardized comparison across studies and over time. Figure 1, adapted from the original CFIR authors [5], shows the scoring system that will be used to score each of the CFIR constructs based on the level of influence they have on the implementation outcome.

Participating Sites

This study is based on a coordinated set of 13 projects, operating on funding from different organizations in Canada, the United States, Kenya, Rwanda, South Africa, and Ethiopia. A cross-section of the 13 current projects will be followed, at regular intervals, as the studies are being completed. The study will take a pragmatic approach and include new projects during the envisioned path to scale and remove or replace projects that do not move forward after collecting all the important data from them regardless of the project outcome.

Figure 1. Scoring system that will be used to score each of the Consolidated Framework for Implementation Research (CFIR) constructs (adapted from the original CFIR authors).



WelTel LTBI (British Columbia)

This is a dually funded project by the BC Lung Association and Canadian Institute of Health Research (CIHR). It evaluates the effect of WelTel on treatment completion among patients with LTBI in an RCT at two TB clinics in British Columbia (Vancouver and New Westminster). The study includes a cost-effectiveness evaluation and stakeholder assessment for health system integration (ClinicalTrials.gov identifier: NCT01549457).

WelTel Retain (Kenya)

This RCT (ClinicalTrials.gov identifier: NCT01630304) aims to assess whether the WelTel intervention improves retention in care in the first year of care after HIV diagnosis in economically disadvantaged cities in Nairobi. The study is funded by the National Institute of Mental Health.

WelTel at Oak Tree (British Columbia)

Following a successful pilot study of the intervention at the Oak Tree Clinic at BC Women's Hospital, additional funding was secured by the Oak Tree team to recruit 100 HIV positive participants for a further evaluation involving clinical outcomes one year before and one year after implementation of the intervention, as well as its cost-effectiveness and health care provider time utilization (ClinicalTrials.gov identifier: NCT02603536).

The Cedar Project (British Columbia)

This project tests the feasibility, acceptability, and efficacy of using WelTel text messages to improve treatment adherence and resiliency for young First Nations people who are HIV-positive or at high risk of HIV. Project sites are in British Columbia and include Vancouver, Prince George, and Chase.

WelTel Big River (Saskatchewan)

The aim of this study is to understand the feasibility and acceptability of implementing the WelTel text messaging program with people living with HIV and hepatitis C in Big River First Nation, Saskatchewan, Canada. A general waiting-room survey will be offered to those who attend the Big River First Nation Health Facility to understand their digital technology use and their attitudes towards communicating with health care providers using these strategies. Pilot study participants will receive check-in messages once a week from an automated platform. The study team will measure if this increased engagement has an impact on the health of participants.

WelTel Kenya2 (Kenya)

This second phase "transition to scale" project, *Changing Global Health One Text at a Time*, is co-supported by Grand Challenges Canada and Amref Health Africa. The aim is to scale-up the WelTel intervention in Kenya's vast northern and arid lands as part of a government-hosted consortium of health-strengthening initiatives, using the Integrated Innovation framework (social, technological, and business innovation). Currently there are five project sites: two in Isiolo County and three in Samburu County.

EmPhAsIS: Empowering Pharmacists in Asthma Management Through Interactive SMS (British Columbia)

This cluster-RCT at 75 pharmacies in British Columbia is designed to examine whether an adaptation of the WelTel intervention into pharmacy services improves adherence to asthma medication. The project site is in Vancouver.

Asthma Telehealth (British Columbia): WelTel eAsthma

The Asthma Telehealth project is a randomized trial testing the adaptation of the WelTel platform to link patients with moderate to severe asthma to their previously validated Asthma Action Plans, thus supporting outpatient self-management.

WelTel HIV (Seattle, USA)

This study is a pilot to assess WelTel in supporting high-needs HIV patients in Seattle and a second pilot for HIV pre-exposure prophylaxis adherence support. It is a National Institute of Health funded project that began in 2016.

WelTel Haida Gwaii (British Columbia)

This pilot implementation uses the WelTel platform and service to support primary care in the Queen Charlotte medical center. It will focus on supporting patient-oriented goals and will be linked to the Northern Health Authority electronic medical record system for remote communities.

WelTel Ethiopia (Gondar, Ethiopia)

This project is piloting implementation of the WelTel platform in clinical care to improve patient engagement in HIV care. The study is taking place at the ART unit of the University of Gondar hospital in rural northern Ethiopia.

WelTel Outreach (British Columbia)

This project is a scale-up program to assess the accessibility, feasibility, and transferability of the WelTel digital platform by the Outreach Team at the BC Centre for Disease Control after their successful use of WelTel LTBI for 3 years.

WelTel South Africa (South Africa)

The aim of this study is to examine the acceptability and feasibility of mHealth/SMS and community-based directly observed ART (cDOT) as interventions to improve ART adherence for preventing mother-to-child HIV transmission in a community primary care setting in Cape Town, South Africa.

Participants

The main participants of this study will be stakeholders, individual project team members, and patients of the different implementations in global settings. Project team members who worked for more than 6 months will be eligible to be study participants to make sure they received enough exposure and experience about the project. For project participants, those who are older than 18 years of old will be included. As per our knowledge, most of the projects have an average of 5 team members to run the intervention. Hence, we target 5 participants for each stage of the assessment per project until saturation is reached.

Project Team Members

The team comprises individuals who are employed (eg, research coordinator, research assistant, statistician, epidemiologist, intern, data analyst), participating in (eg, clinicians who consent participants, respond to participants via the platform, clerical staff who administer questionnaires, operations manager who oversee staff duties) or advising and directing (ie, investigators, research fellows and associates, graduate students) the project.

Stakeholders

Individuals who have a stake in the success or failure of each project may include clinicians not directly involved in the operation of the study, as well as administrators, research participants, privacy and securities experts, government staff interested in mHealth technologies, staff at nongovernmental organizations, policymakers, donors, etc.

Analysis

Our analytic approach will initially focus on the collection of qualitative data, including notes from attendance at project meetings, narratives, and scores compiled through application of the CFIR with project team members. Interview transcripts and notes from the document review will be compiled and reviewed by at least 2 mHealth team members to determine a preliminary coding framework using NVivo. This framework will constantly be reviewed, adapted, and reworked in an iterative manner so as to include data collected from each session and project team. This iterative process will also highlight instances that are unique to specific social and political contexts and that may require further discussion and clarification with project team members.

For the quantitative scoring data, *t* tests, clustering, or repeated measure analysis will be used based on the data to test the relationship between each of the factors and implementation success. By looking at how things were supposed to happen, we will tease out the gap between the ideal and actual result of the research. The gap between research conducted in a controlled setting and the implementation of an intervention or service into a “real-world” environment is often wide. Understanding the relationships between what was supposed to happen and what actually happened will highlight important considerations for implementation. For example, the study protocol might state that a clinician will follow up on all nonresponders with a telephone call. Six months into the study, the realization that most nonresponders are fine and simply “forgot” to respond may prompt a change to the procedure. Going forward, the clerical staff might now assume this role and will triage clinical questions to a nurse. The details outlining what actually happened will provide valuable insight into how the intervention can be integrated into future clinical care. This kind of detailed contextual information will be collected and analyzed across the different projects.

Ethical Considerations

The study protocol, information and consent form, and questionnaires were approved by the University of British Columbia’s Clinical Research Ethics Board (H15-03478) and Behavioral Research Ethics Board (H16-00189), and the Amref Ethics and Scientific Review Committee (AMREF-ESRC

P161/2015). Ethical approval will be renewed on an annual basis. Written informed consent will be sought from interview and focus group participants and those being observed and participating in project study meetings. Meeting participants can indicate to mHealth research team members conducting participant observation that they do not want their comments recorded or that specific topics of a sensitive nature should not be recorded. Those who decline participation will not be included in the study. As a form of member checking, participants will be given the opportunity to review draft reports/articles/summaries of our evaluation. All names will be changed to a participant-chosen pseudonym.

Consent to Participate

Project stakeholders will be identified by each project team. Once a list of names for each project has been generated, the program manager or senior research fellow will email them a description of the study and invite them to participate in the focus group or interview. A copy of the consent form will be included in the email. If they decide they would like to participate, they will be asked to sign a copy of the consent form at the location of the focus group. To attend meetings of projects, the research manager or senior research fellow will ask permission of the principal investigator of each study. They will ask the principal investigator to email the team ahead of time, alerting them to their intention to attend the meeting, and will include the consent form in the email. At the meeting, they will provide a brief description of the study. All of those in attendance who would like to be involved and potentially contacted in the future to participate in an interview will be given a consent form and asked to sign. For those who do not want to participate, no mention of them will be made in the notes taken by the researcher in attendance.

Confidentiality

To maintain participant confidentiality, all identifying information will be removed from questionnaires and study documents. Participants will be identified with a unique clinic identification number that is known only to a limited number of trained clinical and research personnel. Study information containing personal information, such as enrollment and informed consent forms, will be stored in locked filing cabinets offsite with limited access. All personal identifying information will be removed from interview transcriptions. Any information stored on computer databases will be password protected with limited access.

Results

The development of the customized CFIR is completed and currently is in pilot testing. The initial results of the use of the tool in those 13 implementations will be available in 2019. Continuous conference and peer-reviewed publications will be published in the coming years.

Discussion

Principal Considerations

While there are many pilot studies and trials investigating the application of mHealth to improve adherence and other health outcome indicators, such as morbidity and mortality, there is a lack of sufficient evidence to inform the scale-up of mHealth programs in real-world settings. According to Luoto et al [41], ideal evidence for scale-up of mHealth programs includes efficacy (does it work?), effectiveness (does it work in a variety of populations and contexts?), and sustainability (cost effectiveness, demand, adaptation into health system). Following on from this, the overarching goal of our proposed research is, therefore, to close the gap in the evidence required to deliver an effective mHealth service to support patient care at scale in multiple global settings.

Our proposed implementation science study contains four important innovations. First, this study comprises 13 currently funded mHealth projects and programs. As outlined by Edwards et al [42], without attending to context and how it interacts with interventions, implementation of interventions are likely to fail or underperform. Hence our study, based in four countries across two continents, will provide robust, context-specific implementation science evidence to assist in moving the mHealth field forward.

Second, this proposed implementation science study will also compare barriers and facilitators to implementation of mHealth in both high-resource and low-resource settings. Sood et al [43] conducted a systematic review to compare different facilitators and barriers in developed and developing countries for successful electronic medical record implementation and use and found a major difference in barriers in those two settings. However, with respect to the implementation of mHealth interventions, this type of analysis is lacking and this study aims to fill this evidence gap. The results of this study therefore might advance the field of mHealth implementation science by examining predictors of implementation and sustainability as a function of intervention stage, which will give us implementation status based evidence to inform future implementation of similar interventions.

Third, our 13 mHealth projects across the different settings are at different stages. Some are starting, some are in the pilot phase, some are in the transition to scale phase, and some are already adopted as regular programs within the health system. This programmatic variety is a unique opportunity to compare facilitator and barrier factors based on the stage of the project. Additionally, we will be collecting data about the facilitator and barrier factors continuously every 6 months for each of the projects over 5-year period. This will give insight on how the implementation factors change as time advances and at

difference phases of implementation. This will help us generate evidence on barrier and facilitator factors through the beginning, middle, and end of the project periods.

Last, this study will adapt an easy-to-use, pragmatic scoring scheme using the CFIR framework. Overall, this will be one of the first studies to perform cross-project identification of predictors of implementation and sustainability of mHealth in a global setting. After 3 years with substantial data from all 13 sites over time, we will be able to review and make recommendations to adjust and make any necessary improvements to this tool. Our goal is to develop a tool that can be used not only for this project, and by this research group, but by others seeking to implement digital health and global health innovations around the world.

Strengths and Limitations

The proposed study is one of the first to conduct a cross-project examination of individual- and organizational-level predictors of mHealth implementation in global setting. Our menu-of-constructs approach, using the CFIR, is beneficial to frame our study and compare findings with others. However, like other different framework driven studies, there might be some factors that are beyond our capacity to capture. We mitigate this by including a suggestion box under each domain to catch factors that are out of the included constructs in the CFIR framework. The other novel aspect of our approach is the concept of scoring for each of the constructs. However, the scoring will be based on individual perception, which might be biased. We mitigate this by including 5 participants on each of the projects. The other limitation to note is the comparison challenge between sites as different implementations are at different stages and different disease domains. We will mitigate this limitation by collecting data continuously during the entire phase of the project and perform the comparison analysis when the projects are in a similar stage.

Conclusions

Many interventions found to be effective in health services research studies fail to translate into meaningful patient care outcomes across multiple contexts in settings outside the RCT environment. The conventional wisdom is that two-thirds of organizations' efforts to implement change fail. In mHealth, there is no concrete evidence on the level of success and failure and why that happens. Our implementation science evaluation will fill a major void in this rapidly emerging field by identifying facilitators and barriers of mHealth success or failure. The evidence generated will help us document in a structured way the lessons learned by each project team and will identify how this information can inform the scale-up of mHealth interventions across diverse settings in Africa and North America, and ultimately beyond.

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Conflicts of Interest

The technology platform (WelTel/SMS) has been developed by a nonprofit organization, WelTel mHealth Society, and a private company, WelTel Incorporated. RL has financial as well as professional interests in both organizations.

Multimedia Appendix 1

CIHR peer-review report.

[\[PDF File \(Adobe PDF File\), 35KB - resprot_v7i7e162_app1.pdf\]](#)

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Abbreviations

ART: antiretroviral therapy
cDOT: community-based directly observed antiretroviral therapy
CIHR: Canadian Institute of Health Research
CFIR: Consolidated Framework for Implementation Research
UNAIDS: Joint United Nations Programme on HIV and AIDS
LTBI: latent tuberculosis infection
mHealth: mobile health
SMS: short message service
RCT: randomized controlled trial
TB: tuberculosis
WHO: World Health Organization

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Original Paper

Scholarly Influence of the Conference and Labs of the Evaluation Forum eHealth Initiative: Review and Bibliometric Study of the 2012 to 2017 Outcomes

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Abstract

Background: The eHealth initiative of the Conference and Labs of the Evaluation Forum (CLEF) has aimed since 2012 to provide researchers working on health text analytics with annual workshops, shared development challenges and tasks, benchmark datasets, and software for processing and evaluation. In 2012, it ran as a scientific workshop with the aim of establishing an evaluation lab, and since 2013, this annual workshop has been supplemented with 3 or more preceding labs each year. An evaluation lab is an activity where the participating individuals or teams' goal is to solve the same problem, typically using the same dataset in a given time frame. The overall purpose of this initiative is to support patients, their next of kin, clinical staff, health scientists, and health care policy makers in accessing, understanding, using, and authoring health information in a multilingual setting. In the CLEF eHealth 2013 to 2017 installations, the aim was to address patient-centric text processing. From 2015, the scope was also extended to aid both patients' understanding and clinicians' authoring of various types of medical content. CLEF eHealth 2017 introduced a new pilot task on technology-assisted reviews (TARs) in empirical medicine in order to support health scientists and health care policymakers' information access.

Objectives: This original research paper reports on the outcomes of the first 6 installations of CLEF eHealth from 2012 to 2017. The focus is on measuring and analyzing the scholarly influence by reviewing CLEF eHealth papers and their citations.

Methods: A review and bibliometric study of the CLEF eHealth proceedings, working notes, and author-declared paper extensions were conducted. Citation content analysis was used for the publications and their citations collected from Google Scholar.

Results: As many as 718 teams registered their interest in the tasks, leading to 130 teams submitting to the 15 tasks. A total of 184 papers using CLEF eHealth data generated 1299 citations, yielding a total scholarly citation influence of almost 963,000 citations for the 741 coauthors, and included authors from 33 countries across the world. Eight tasks produced statistically significant improvements (2, 3, and 3 times with $P < .001$, $P = .009$, and $P = .04$, respectively) in processing quality by at least 1 out of the top 3 methods.

Conclusions: These substantial participation numbers, large citation counts, and significant performance improvements encourage continuing to develop these technologies to address patient needs. Consequently, data and tools have been opened for future research and development, and the CLEF eHealth initiative continues to run new challenges.

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KEYWORDS

evaluation studies as topic; health records; information extraction; information storage and retrieval; information visualization; patient education as topic; speech recognition; systematic reviews; test-set generation; text classification

Introduction

The requirement to assure that patients can understand their own care epicrisis, discharge summaries, and other electronic health (eHealth) records are stipulated by policies and laws ([Multimedia Appendix 1](#)) [1]. For example, the Declaration on the Promotion of Patients' Rights in Europe in 1994 by the World Health Organization states that all patients have the right to be fully informed about their own health status, prognosis, medical conditions, diagnoses, proposed and alternative treatment with potential risks and benefits, effects of nontreatment, treatment progress, and discharge guidelines. It also obligates health care workers to give every patient a written summary of this information and communicate it in a way appropriate to the patient's capacity for understanding, including minimal use of unfamiliar jargon.

However, patients, their next of kin, and other laypersons are likely to experience difficulties in understanding the arcane jargon of eHealth records, and improving this readability can contribute to patient empowerment [2], defined as providing partial control and mastery over health and care which leads to patients having an active role in their health care, making better health/care decisions, being more independent from health care services, and having decreased costs of care [3]. This could mean replacing jargon words with patient-friendly synonyms, expanding shorthand, and providing an option to see the original text ([Figure 1](#)). Medical Subject Headings (MeSH), Systematized Nomenclature of Medicine–Clinical Terms (SNOMED CT), Unified Medical Language System (UMLS), and other terminology standards can help to define synonym replacements, but automated language processing is needed to identify text snippets to be replaced with synonymous snippets.

Patient-friendly language in health records can help patients make informed decisions, but this also depends on their access to consumer leaflets and other further supportive information about their health concerns. The internet is a powerful source for this information; most people will turn to its large range of

content that is widely accessible and searchable [4,5]. However, layperson searches for medical information online can lead to the escalation of concerns and consequent anxiety [6]. Hence, helping patients retrieve relevant, understandable, and reliable information on the internet is crucial.

Web-based eHealth records provide a way to bridge patients' actions of reading their own eHealth records with them searching the internet for further information. These eHealth records are targeted to both patients and health care workers for reading, writing, and sharing information [7]. Combined with the aforementioned record processing, this could mean enriching the health record with hyperlinks to term definitions, care guidelines, and other information on patient-friendly and reliable sites on the internet ([Figure 1](#)) as one way to facilitate patients in understanding their health and health care [2].

This paper reports on the 6 installations of CLEF eHealth, organized as part of the Conference and Labs of the Evaluation Forum (CLEF) initiative from 2012 to 2017. In 2012, it ran as a scientific workshop with the aim of establishing an evaluation lab, and since 2013, this annual workshop has been supplemented with 3 or more preceding labs each year. An evaluation lab is an activity where the participating individuals or teams' goal is to solve the same problem, typically using the same dataset in a given time frame. In the CLEF eHealth 2013 to 2017 installations, the aim was to address patient-centric text processing. From 2015, the scope was also extended to aid both patients' understanding and clinicians' authoring of various types of medical content. CLEF eHealth 2017 introduced a new pilot task on technology-assisted reviews (TARs) in empirical medicine in order to support health scientists and health care policymakers' information access.

Our focus in this article is on measuring and analyzing the scholarly influence of CLEF eHealth from 2012 to 2017. Its citation analysis, problem specifications, evaluation methods, data releases, software releases and submissions, and participation and benchmark results are addressed.

Figure 1. Original text, its enrichment, and submission statistics from the Conference and Labs of the Evaluation Forum (CLEF) eHealth 2013 evaluation lab. The year of 2013 has been chosen as an example here to illustrate the outcomes of the first year of organizing CLEF eHealth evaluation lab. SNOMED CT: Systematized Nomenclature of Medicine–Clinical Term, UMLS: Unified Medical Language System.



From:

80 y/o male with 2 yr h/o SOB and GERD. Had Echo that revealed AS. Has had serial echo's since, with the last done on [...] which showed worsening AS.

To:

80 year old (y/o) male with 2-year (yr) history of (h/o) **shortness of breath**²⁶⁷⁰³⁶⁰⁰⁷(SOB, [definition](#), [treatment guidelines](#)) and **heartburn**^{C0018834} (also known as **gastroesophageal reflux disease** (GERD, [definition](#), [treatment guidelines](#))). Had a **diagnostic ultrasound of heart** (**echocardiogram**^{169241000 = Echocardiogram abnormal})^{C0810219} (echo/Echo) that revealed **aortic valve stenosis**⁶⁰⁵⁷³⁰⁰⁴ (AS, [definition](#), [treatment guidelines](#), [guidelines on separating the symptoms of heart conditions from heartburn](#)). Has had serial **diagnostic ultrasound of heart** (**echocardiogram**¹⁶⁹²⁴¹⁰⁰⁰)^{C0810219}'s since, with the last done on [...] which showed worsening **aortic valve stenosis**⁶⁰⁵⁷³⁰⁰⁴.

113 submitted systems

- **Disorder boundaries**
 - 22 teams
 - F1 = 75% (Precision = 80%, Recall = 71%)
- **Disorder coding** (SNOMED CT)
 - 17 teams
 - Accuracy = 59%
- Shorthand expansion and **preferred-term selection** (UMLS)
 - 5 teams
 - Accuracy = 72%
- **Hyperlinking** using 1) patient or next-of-kin's information need, document preferences, and assessment on the content reliability and 2) about 1 million documents from health and medicine sites
 - 9 teams
 - Precision@10 = 52%

Methods

The scholarly influence of the CLEF eHealth installations from 2012 to 2017 was measured by conducting a bibliometric study—an established method to provide a quantitative and qualitative indication of scientific activities whose use is also emerging in the context of evaluation initiatives [8-10]—of the related publications and their citations received by October 31, 2017. This study consisted of publication data collection, citation data collection, and data analysis.

The first 2 out of these 3 standard steps were concerned with the collection of materials for the measurement. First, conference paper and working note (ie, technical reports) publication data relevant to CLEF eHealth was collected from the CLEF proceedings (see [Multimedia Appendix 2](#)). These were supplemented with author-declared papers that extend these publications or otherwise use the CLEF eHealth datasets. Then, citation data for the resulting publication data were collected on October 26, 2017, from Google Scholar, one of the most comprehensive citation data sources in general and in particular for computer science, which is the main field of many CLEF eHealth scientists.

The third step formed the method of the study. Namely, citation content analysis [11], founded on content analysis [12] and grounded theory (introduced in the 1960s) [13], was used for the data analysis. This allowed a systematic, replicable compression of materials from the first 2 steps as codes and testing of hypotheses about the quantity and quality of the scholarly influence of CLEF eHealth from 2012 to 2017. Citation content analysis was chosen over the more established content analysis (Google Scholar had over 15,000 citations for the aforementioned paper [12] about this method) and grounded theory (Google Scholar had nearly 400 citations of the 2007 revision [13] of grounded theory for health sciences) because it combined these 2 research techniques for interpreting meaning from the content of text data as 1 overarching method for content coding of scientific literature and analysis of the codified content.

Using Google Scholar for citation data collection in bibliometric studies had at least 2 shortcomings [14-16]: first, paper

duplication as a citation entry was frequent, for example, due to misspellings or incorrectly identified years and would, without manual refinement, cause errors in the counts. Another source for counting errors was incorrect automated merging of citation entries because of the same or almost the same title of a given conference paper and its journal extension. Similar to the scholarly influence measurement of CLEF 2000–2009 [9], our citation counts by Google Scholar were reviewed and refined for these 2 shortcomings by hand.

As part of the citation content analysis, the included publication and citation data were codified for 10 content categories: participation (including both expression of interest [EOI] and submission), author, affiliation, problem specification, evaluation method, benchmark result, data release, software launch, demonstration system, and citation. Similar to the bibliometric study [9], attention was paid not only to the number of citations but also the number of authors, their affiliations, and countries of affiliation. In order to illustrate the influence to the scholarly community and the individual scholars (because most participating teams included graduate students and/or early career academics), the scholarly influence was computed by multiplying the number of citations (ie, 1299, also known as scholarly impact [8-10]) for the included 184 papers by the number of their coauthors (ie, 741).

Results

Citation Analysis From 2012 to 2017

The topic of patient-friendly multilingual communication formed the focus of CLEF eHealth from 2012 to 2017 and generated a total scholarly influence of 962,559 citations (and scholarly impact of 1299 citations) for the 184 CLEF eHealth papers and reached 741 authors from 33 countries across the world ([Multimedia Appendix 3, Figure 2](#)) [17-22]. Of the 184 papers, 143 (77.7%) had been cited at least once and the maximum, mean, median, and standard deviation of citations per paper were 147, 7, 3, and 15, respectively. The h-index (ie, the number of papers each of which with at least h citations) and i10-index (ie, the number of papers with at least 10 citations) were 18 and 35, respectively. The annual number of published papers was 16, 35, 34, 31, 33, and 35 in 2012, 2013, 2014, 2015, 2016, and

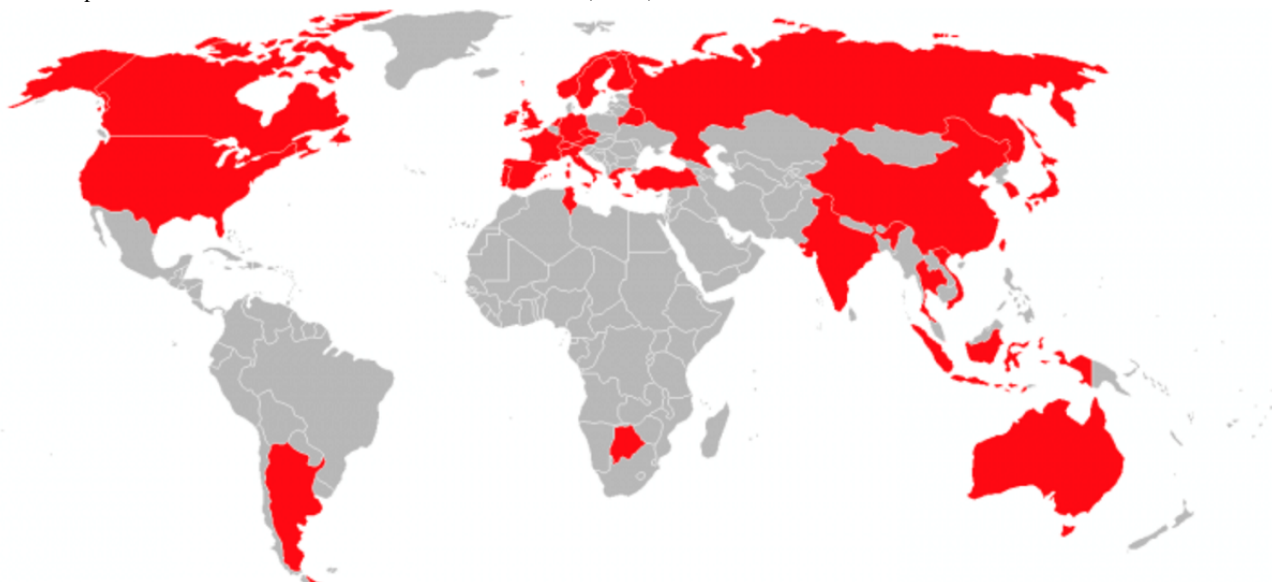
2017, respectively. Although a clear 158 majority of the 184 papers were working notes (85.9%), 22 conference papers (12.0%) and 4 journal papers (2.0%) were also published.

In accordance with the CLEF eHealth mission to foster teamwork, the number of coauthors per paper was 4 on average, with a maximum, median, minimum, and standard deviation of 15, 3, 1, and 3, respectively. In 47 out of the 184 papers (25.5%), this coauthoring collaboration was international and sometimes even across continents (ie, Africa–Europe, Asia–Australia, Asia–Europe, Asia–North America, Australia–Europe, Australia–Europe–North America, and Europe–South America). Of the 466 author organizations, 427 (91.6%) were academic; 21 (4.9%) government and 18 (4.2%) industry organizations participated from 2012 to 2017.

CLEF eHealth particularly welcomed and attracted multidisciplinary teams to collaborate and bridge the researchers,

scientists, lecturers, and graduate students with engineers, practitioners, and policy makers. For example, the 33 working notes and 1 conference paper from the CLEF eHealth 2013 evaluation lab [18] included 162 authors from 10 countries and featured some leading organizations in health information management, extraction, and retrieval, including National Information and Communications Technology Australia (NICTA), Commonwealth Scientific and Industrial Research Organization, and Health Language Laboratories from Australia; Chinese Canon Information Technology; French National Center for Scientific Research; Indian RelAgent Private Lt; US National Center for Biotechnology Information, Kaiser Permanente, and Mayo Clinic; and universities from Australia, China, Finland, Ireland, Republic of Korea, Spain, Sweden, United Kingdom, and United States. They represented academic, government, and industrial research labs, large technology corporations and smaller businesses, and health care providers and insurers.

Figure 2. Map of the Conference and Labs of the Evaluation Forum (CLEF) eHealth 2012 to 2017 authors' affiliation countries in red.



Problem Specifications From 2013 to 2017

The first installations of the lab, held in 2013 and 2014, focused on text processing, search, and visualization to ease patients' (or their next of kin) understanding of hospital discharge summaries. Each year, 3 tasks were organized.

The 2013 tasks 1a and 1b considered disorder naming (eg, heartburn as opposed to gastroesophageal reflux disease) by identification of disorder names and normalization of the identified names by translating them to patient-friendly synonyms. These tasks could be illustrated as follows: the system should first automatically recognize GERD as a named entity in the phrase "80 y/o male with 2 yr h/o GERD," associated with the entity code in SNOMED CT. Then, it should map the code to its most patient-friendly entry term, being heartburn as opposed to gastroesophageal reflux disease in the example phrase.

The 2013 task 2 on shorthand expansion aimed at mapping clinical abbreviations and acronyms to patient-friendly synonyms (eg, automatically expanding and mapping the 3 italicized text snippets in "80 y/o male with 2 yr *h/o SOB* and

GERD" to history of, shortness of breath, and heartburn, respectively). Instead of actually writing the disorder names and shorthand expansions in the 2013 tasks 1b and 2, the respective SNOMED CT and UMLS codes (eg, GERD got the SNOMED CT code C0017168 in task 1b and UMLS code C0018834 in task 2) were applied. These coding systems were chosen because they are among the most commonly used in clinical settings.

This challenge continued in the 2014 task 2 on template filling, with the aim of developing attribute classifiers that predict the values of the UMLS concept unique identifiers (CUIs) with mention boundaries. The disease/disorder templates consisted of the following 10 attributes: negation indicator, subject class, uncertainty indicator, course class, severity class, conditional class, generic class, body location, DocTime class, and temporal expression.

The 2013 task 3, 2014 task 3, and 2014 task 1 supplemented the processing of health records with information from the internet, based on the patient's (and next of kin's) information needs associated with the records. The 2013 and 2014 task 3 on information search (information retrieval [IR]) would, for

example, find the definition of shortness of breath, treatment guidelines for heartburn, and guidelines on separating the symptoms of heart conditions from heartburn for the health record with the aforementioned sentence. The challenge also considered in 2014 the problem of an individual expressing their information need in a non-English language, for search on Web pages written in English. Support of this functionality is important given the large proportion of Web medical content written in English. The 2014 task 1 on interactive information visualization had the overall goal of designing an effective, usable, and trustworthy environment for navigating, exploring, and interpreting health information as needed to promote understanding and informed decision making. It was divided into 2 parts as linkages to the three 2013 tasks, with tasks 1 and 2 on text classification as the first part and task 3 on IR as the second part. The scenario of the 2014 task 1 was an English-speaking, discharged patient (or next of kin) in their home in the United States. By reading their discharge document and further information on the internet on either a networked desktop system or mobile device (eg, mobile phone or tablet), they wanted to learn about their own health and health care in general and clinical treatment history, current symptoms and developments, and future implications in particular.

In 2015 and 2016, CLEF eHealth expanded its scope to multilingual text processing, medical Web search, and speech-to-text conversion to ease both patients (and their next of kin) and clinicians' understanding of various types of medical content. Again, 3 tasks per year were organized.

The 2015 and 2016 task 1 built on processing tasks, data, and software by considering its nursing handover report support [23]. In clinical handover between nurses, verbal handover and note-taking could lead to loss of information, and electronic documentation was seen as laborious, taking time away from patient education. The challenges addressed taking clinical notes automatically by using speech recognition (SR) to convert spoken nursing handover into digital text and using information extraction (IE) to fill out a handover form.

The 2015 and 2016 task 2 considered clinical named entity recognition on French texts, previously an unexplored language. They aimed to automatically identify clinically relevant entities from French biomedical articles. In addition, the 2016 task also addressed extracting causes of death from French death reports.

The 2015 and 2016 task 3 considered cross-lingual medical search on the Web. They focused on trying to retrieve relevant and reliable Web pages that meet a given patient's (or their next of kin's) general information needs related to their medical complaints (eg, their need to understand a condition or the cause of a medical symptom). The tasks also considered information needs that were expressed in several non-English languages.

In 2017, the following 3 tasks were organized to continue the 2016 tasks 2 and 3 and introduce a new pilot task: 2017 task 1 explored the problem of multilingual text processing by considering the extraction of causes of death from both French and English death reports to ease clinicians' understanding of these reports. The 2017 task 3 developed medical Web search techniques to address the challenge posed by patients (or their next of kin) in locating relevant and reliable medical content

on the Web. In addition, the 2017 task 2 considered a new challenge, that of TAR generation in empirical medicine to support health care and policy making. Medical researchers and policy makers, while writing systematic review articles (eg, covering the treatment of a condition), must ensure that they consider all documents relevant to their review. As the size of medical libraries continues to expand, automation in this process is necessary.

Evaluation Methods From 2013 to 2017

The evaluation criterion in the 2013 task 1a on disorder identification was the correctness in identification of disorder text snippets as defined by the F1 measure with a nonparametric test called random shuffling for the statistical significance assessment on 100 annotated health records for testing. An independent set of 200 annotated health records was provided for training. When computing true positives for the exact F1, the snippets by the solution-system and hand-annotation had to be identical, while an overlap was enough for the relaxed F1.

The evaluation criterion in the 2013 task 1b on disorder normalization was the correctness in mapping the disorders to SNOMED CT codes as defined by the accuracy measure with random shuffling for the statistical significance assessment. The annotated health records and their split between training and testing were the same as in task 1a. When computing true positives for the exact accuracy, the total number of code mappings was computed from the annotated records and the system was penalized for missing codes the same way as for incorrect codes. For the relaxed accuracy, the system was only evaluated on annotations that were detected by the system—that is, the total number corresponds to the code mappings with strictly correct text snippet generated by the system.

The evaluation criterion in the 2013 task 2 on shorthand extension was the correctness in mapping the preidentified shorthand to UMLS codes. This criterion was formalized using the exact and relaxed accuracy measures with random shuffling for the statistical significance assessment. The annotated health records and their split between training and testing were the same as in task 1a.

Evaluation of submissions to the 2013 task 3 on IR was conducted with respect to the relevance of the retrieved documents to the information seeker on 50 test queries and the matching result set. The official primary and secondary measures were the precision at 10 (P@10) and normalized discounted cumulative gain at 10 (NDCG@10), respectively. The Wilcoxon test was used to better compare the measure values for the runs and benchmark.

In the 2014 task 1 on information visualization, participants could submit their designs to an optional draft submission to receive comments, followed by the call for final submissions. Final submissions were judged on their rationale for the design, including selection of appropriate visual interactive data representations and reference to state-of-the-art techniques by an expert panel with 5 members. To be successful, the submission had to demonstrate that the posed problems and information needs are addressed, provide a compelling use-case driven discussion of the work flow supported and exemplary

results obtained, and highlight the evaluation approach and obtained findings. Primary judging criteria included the effectiveness and originality of the proposed design that were further divided to categories for aesthetics, interaction, usability, and visualization.

Evaluations in the 2014 tasks 2 and 3 followed the 2013 practices. In the 2014 task 2 on template filling, exact and relaxed versions of accuracy and F1 were used. In the 2014 task 3 on IR, participants were provided with 50 topics, including 5 training topics, with their translation in Czech, German, and French. Primary and secondary evaluation measures were P@10 and NDCG@10, respectively.

The 2015 task 1 on speech recognition evaluation used error in speech recognized words, and 100 training and 100 test documents were provided.

The 2015 task 2 on named entity recognition had 3 subtasks that were evaluated separately: (1) for plain entity recognition, raw text was supplied to participants who had to submit entity annotations comprising entity offsets and entity types, (2) for normalized entity recognition, raw text was supplied to participants who had to submit entity annotations comprising entity offsets, entity types, and entity normalization (UMLS CUIs), and (3) for entity normalization, raw text and plain entity annotations were supplied to participants who had to submit entity normalization (UMLS CUIs). For each of the subtasks, the system output on the unseen test set was compared to the gold standard annotations, and precision, recall, and F1 were computed.

In 2015 task 3 on IR, evaluation was conducted using similar measures as previous years: P@10 and NDCG@10 were the primary and secondary measures, respectively. A separate evaluation was conducted using both relevance assessments and readability assessments. For all runs, rank-biased precision was computed along with its readability-biased modifications for the binary readability assessments and the graded readability assessments.

In 2016, the nursing handover support task used precision, recall, and F1 for evaluation. Performance was evaluated first separately in every heading from 1 to 35 and the 36th heading for irrelevant text. Then, the performance was averaged over the 35 form headings and also documented in the dominant class of 36. The Wilcoxon test was used for statistical significance testing. The previous 200 training and test documents were provided for training; they were supplemented by another 100 documents for testing.

For the 2016 task 2 and 2017 task 1 on IE, the system output on the unseen test set was compared to the gold standard annotations, and precision, recall, and F1 were compared. After submitting their result files, participating teams had 1 extra week to submit the system used to produce them or a remote access to the system, along with instructions on how to install and operate the system for the replicability to be tested.

In 2016 and 2017, for the IR task, evaluation was conducted using P@10 and NDCG@10 as the primary and secondary measures, respectively. Precision was computed using the binary relevance assessments; NDCG was computed using the graded

relevance assessments. A separate evaluation was conducted using the multidimensional relevance assessments (topical relevance, readability, and trustworthiness). For all runs, rank-biased precision was computed along with its multidimensional modifications for the binary readability assessments, the graded readability assessments, and the binary readability and trustworthiness assessments. In 2017, these measures were parameterized for a given user's expertise.

In the 2017 pilot task on TAR in empirical medicine, evaluation measures were area under the recall-precision curve, minimum number of documents returned to retrieve all relevant documents, work saved over sampling at different recall levels, area under the cumulative recall curve normalized by the optimal area, recall @ 0% to 100% of documents shown, a number of newly constructed cost-based measures, and reliability.

Data Releases From 2013 to 2017

The CLEF eHealth 2013 tasks used the 300 deidentified, manually annotated (for disorder names and clinical shorthand) health records of the Shared Annotated Resources (ShARe) corpus of the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC) II database, consisting of discharge summaries and electrocardiogram, echocardiogram, and radiology reports.

To enable IR, 55 new search topics were formed specifically for task 3. Each search task was described using a patient profile (eg, a 40-year-old woman, who seeks information about her condition), information need (eg, description of what type of disease hypothyroidism is), and query with separate fields for its title (eg, Hypothyroidism) and description (eg, What is hypothyroidism?). The profile also allowed the participants to address the task without considering the aforementioned health records. To create result document sets for these search tasks, a large crawl of online health resources targeted to laypeople and clinicians and provided by the Knowledge Helper for Medical and Other Information users (Khresmoi) project was used.

The CLEF eHealth 2014 task 1 built on these 2013 datasets by combining them as a whole in order to address information search and visualization in a patient-centric way. One mandatory and 5 optional patient cases were carefully chosen from the 2013 tasks 1 to 3 for this task [24]. These consisted of search topics and result sets from task 3 and associated annotated discharge summaries from tasks 1 and 2.

The 2014 task 2 on template filling also used the 2013 dataset of 300 deidentified health records, supplemented by a test set of 133 unseen discharge documents and new expert annotations created as part of the ShARe project. The annotations extended the existing disorder annotations from the 2013 task 1 by focusing on template filling for 10 different attributes for each disorder mention.

To enable IR in the 2014 task 3, 55 new queries were first formulated by experts from the main disorders diagnosed in discharge summaries provided in the 2014 task 2 and then associated with result document sets of the aforementioned Khresmoi set. Participants were provided with the mapping between queries and discharge summaries and were again given an option to use the discharge summaries.

The CLEF eHealth 2015 and 2016 targeted 2 new tasks as its tasks 1 and 2, in addition to continuing its established and popular series of IR tasks as its task 3. The new task 1 focused on supporting handover communication with 300 synthetic patient cases for the SR training, validation, and testing in 2015 and IE training, validation, and testing in the 2016 task 1. Each case in this NICTA Synthetic Nursing Handover Data consisted of a patient profile; a written, free-form text paragraph (ie, the written handover document) to be used as a reference standard in SR; and its spoken (ie, the verbal handover document) and speech-recognized counterparts. The written handover documents were annotated by a registered nurse using a form with 49 headings (ie, classes) to fill out.

For the new 2015 and 2016 task 2, two types of biomedical documents were used: a total of 1668 titles of scientific articles indexed in the MEDLINE database and 6 full-text drug monographs published by the European Medicines Agency. These were annotated with 10 types of entities of clinical interest defined by semantic groups in the UMLS. The expert annotations marked each relevant entity mention in the documents and assigned the corresponding semantic types and CUIs. The 2016 task 2 also featured a subtask that used the CépiDC Causes of Death Corpus with free-text descriptions of causes of death as reported by physicians in the standardized causes of death forms. Each document (65,843 death certificates in total) was manually annotated by experts with the codes from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) per the international World Health Organization standards. Manually built dictionaries of terms associated with the annotated ICD-10 codes were also released.

The 2015 task 3 considered the following scenario to generate 67 English queries: a patient or their next of kin is first shown images and videos related to medical symptoms and then asked which queries they would issue to a Web search engine if they were exhibiting such symptoms and wanted to find more information to understand these symptoms or their condition. In 2016, 6 queries were generated for each information need by having individuals with different levels of medical expertise formulate queries based on the content of posts extracted from the askDocs section of the Reddit public health Web forum. For the multilingual query set, queries were translated by experts to Arabic, Czech, German, Farsi, French, Italian, and Portuguese in 2015 and Czech, German, French, Hungarian, Polish, and Swedish in 2016. The Khresmoi document collection was used in 2015, and a new document collection, ClueWeb12 B13, in 2016. Along with relevance assessments by expert assessors on the result document sets, readability judgements were also collected for the assessment pool in 2015 and both readability and reliability in 2016.

Finally, in 2017, the CLEF eHealth 2016 tasks 1 and 3 were extended and the aforementioned new pilot task with unseen data was introduced as the CLEF eHealth 2017 task 2. The 2017 task 1 used a corpus of expert-annotated death certificates from France in French and the United States in English with respect to the ICD-10 codes. Again, this task supplemented its data releases by manually built dictionaries of terms associated with the annotated ICD-10 codes. The 2017 task 3 used the same

document collection and topics as in 2016, with the aim of acquiring more relevance assessments and improving the collection reusability.

The new TARs in empirical medicine task (ie, the 2017 task 2) used a subset of MEDLINE documents for its challenge to make abstract and title screening more effective. The PubMed identifiers (PMIDs) of potentially relevant MEDLINE document abstracts indexed by the PubMed search engine were provided for 20 training and 30 test topics. The PMIDs were collected by the task coordinators by rerunning the MEDLINE Boolean query used in the original systematic reviews conducted by Cochrane to search PubMed. Topics consisted of the Boolean search from the first step of the systematic review process: a topic identifier; title of the review, written by Cochrane experts; Boolean query manually constructed by Cochrane experts; and set of PMIDs returned by running the query in MEDLINE. The original systematic reviews written by Cochrane experts included a reference section that listed included, excluded, and additional references to medical studies. The union of included and excluded references were the studies that were screened at a title and abstract level and considered for further examination at a full content level. These constituted the relevant documents at the abstract level, while the included references constituted the relevant documents at the full content level. References in the original systematic reviews were collected from a variety of resources, not only MEDLINE. Therefore, studies that were cited but did not appear in the results of the Boolean query were excluded from the label set.

Software Releases and Submissions From 2013 to 2017

CLEF eHealth began providing participants with software and code for method evaluation, record text annotation, and document relevance assessment in 2013 and extended this to also release processing code in 2016. The software and code releases were motivated by our desire for faster progress, comprehensive benchmarking, and transparency of the CLEF eHealth outcomes. Prior to CLEF eHealth, the progress in eHealth information and communication technology (ICT) was extremely limited in comparison to banking, defense, and many other fields that also record big data and benefit from their analytics because of barriers in limited collaboration in sharing data, processing methods, and evaluation outcomes together with their common conventions and standards [25].

In the CLEF eHealth 2013 tasks 1 and 2, we released both a command-line tool and a graphical user interface that the participants could use to compute the values for the official and supplementary evaluation measures and visualize annotations against their method outputs. This eHOST annotation tool [26] also supported participants in annotating more data, although methods using teams' own annotations were evaluated separately from those based on the organizers' original annotations alone. In the CLEF eHealth 2013 task 3, we released the Relevation! relevance assessment tool [27] and provided participants with a pointer to an established tool for computing values for the official and supplementary evaluation measures.

The 12 CLEF eHealth 2014 to 2017 tasks in total continued releasing software and code for computing values for evaluation measures, evaluating statistical significance of their differences

between 2 or more methods, data annotation, and relevance assessment. In addition to releasing purpose-built software and code for the tasks, pointers to such helpful resources by other tasks and groups were also catalogued and provided on the website and overview paper of each task.

The CLEF eHealth 2016 task 1 released the organizers' entire software stack as a state-of-the-art solution to the handover IE problem (ie, both feature generation and IE) [23]. Participants were welcomed but not mandated to use the released code and, as intended, the results highlighted all participating teams' methods outperforming this known state-of-the-art baseline.

In parallel to these software and code releases, CLEF eHealth established its replication track in 2016. The track gave the participants of the 2016 task 2 and 2017 task 1 the opportunity to submit their processing methods to organizers, who then attempted to replicate the run submissions. In 2016, 3 participating teams chose this option and submitted a total of 7 methods, all of which the organizers were able to replicate perfectly. In 2017, 5 participating teams chose the replication track and submitted a total of 22 methods. The organizers were able to replicate most of them perfectly without contacting the teams. Where team contact was required, replication was achievable after further technical clarification on system requirements, installation procedure, and practical use. The organizers also reported an overall improvement in method documentation as an outcome of running the track twice.

Participation and Benchmark Results From 2013 to 2017

The CLEF eHealth lab each year from 2013 to 2017 attracted more than 100 teams to submit their EOI for the task and among them, 20 to 34 teams participated (Multimedia Appendix 3). The difference between the number of teams interested and the actual participation was explained by the ease of the registration process versus the substantial amount of work required to actually submit to these difficult tasks. The very high number of EOIs within the first 2 years was surely related to the novelty of the 2013 and 2014 tasks. The number of participants from 2013 to 2017 remained stable over the years despite the regular change and diversity in tasks. The most popular tasks were related to the IR task 3 in 2013 to 2017. Given that both the number of EOIs and participants have decreased for the last 2 years, the task might have to be redefined.

The results of the 15 tasks organized as part of the CLEF eHealth lab from 2013 to 2017 contributed to the body of knowledge about the difficulty of health information management, extraction, and retrieval (Multimedia Appendix 4). In addition, the methodological diversity of the submissions shown by more than 100 teams all over the world, together with the baselines by the organizers, addressed the applicability of particular methods. Eight tasks produced statistically significant improvements in processing quality by at least 1 of the top 3 methods.

Discussion

Principal Findings

The CLEF eHealth installations have offered 15 evaluation labs in the fields of medical information management, extraction, and retrieval since 2012. Evaluation methods and resources have been developed and shared with the community to support the understanding of and access to medical content by laypeople (or their next of kin), clinicians, scientists, and policy makers. Evaluation results for the methods and resources developed have been released to the community. In doing so the lab has provided an evaluation setting for the progression of research in multilingual medical ICT. This has facilitated further evaluation into medical system development for information management, extraction, and retrieval and aiding the progression of research in these areas.

The annual CLEF eHealth lab workshop held at the main CLEF conference provides for the dissemination and discussion of the outcomes of each year's challenges. This has facilitated discussion in the community, cross-fertilization of ideas, and further progress in the medical information production, processing, and consuming ecosystem. Each year the lab organizers produce lab overview papers describing the challenges offered and participants' results. These have proven influential, as indicated by their citation indexes.

Comparison With Prior Work

At least 12 years prior to establishing CLEF eHealth in 2012, evaluation labs began addressing limited collaboration as a major barrier that hinders the transfer of ICT for processing free-form text to clinical practice, and this is evidenced by improvements in developing and sharing data, community conventions, standards, software, and evaluation benchmarks [25]. The other 2 identified main barriers were absence of user centricity in technology development and inability to replicate results. By definition as a lab, CLEF eHealth 2012–2017 continued contributing to the barrier of limited collaboration but used the remaining 2 barriers to distinguish itself from other labs. Namely, it placed layperson patients (as opposed to clinical experts) as targeted technology users to the center of the shared tasks in 2013 and introduced its replication track in 2016.

The CLEF initiative began in Europe in 2000, and at the same time that the first CLEF eHealth evaluation lab with 3 shared tasks was launched in 2013, the CLEF Question Answering for Machine Reading lab introduced a pilot task on machine reading on biomedical text about Alzheimer disease [28]. Extending the prior work inclusion criterion from text to other data modalities, the ImageCLEF lab included annual shared tasks on biomedical image processing from 2005 to 2013 [29–31].

Before CLEF, the Text Retrieval Conference (TREC) was established in the United States in 1992 as an evaluation initiative with evaluation labs of shared tasks leading to annual conferences and workshops. In 2000, the TREC filtering tasks considered user profiling to filter in only the topically relevant biomedical abstracts using MeSH as topics [32]. From 2003 to 2007, the TREC genomics tasks ranged from ad hoc IR to text classification, passage retrieval, and entity-based question

answering on data from biomedical papers and eHealth records [33]. In 2011 and 2012, the TREC medical records tasks targeted building a search engine where the patient cohort's eligibility criteria of a given clinical study can be specified through the search query, and then after information search on English eHealth records, the matching population is returned for study recruitment purposes [34]. This paper had 17 citations by July 6, 2018.

The NII Test Collection for Information Retrieval Systems was launched in Japan in 1997 as an evaluation initiative and in 2013, its medical natural language processing lab considered the following 3 shared tasks on Japanese eHealth records [35]: text deidentification, complaint/diagnosis IE, and an open challenge, where participants were given the freedom to try to solve any other task on the dataset that was used for the first 2 tasks. This paper gathered 33 citations by July 6, 2018.

The Informatics for Integrating Biology and the Bedside initiative, begun in the United States in 2006, addressed clinical text processing through its following shared tasks on English-language eHealth records from 2006 to 2012 [36]: text deidentification and identification of smoking status in 2006; recognition of obesity and its comorbidities in 2008; medication IE in 2009; concept, assertion, and relation recognition in 2010; co-reference analysis in 2011; and temporal-relation analysis in 2012. This paper had 491 citations by July 6, 2018.

The Medical Natural Language Processing Challenges, launched in the United States in 2007, considered automated diagnosis coding of English-language radiology reports from a children's radiology department in 2007 and classifying the emotions found in English-language suicide notes in 2011 [37,38]. These papers were cited in total 603 times by July 6, 2018.

The annual SemEval/Senseval Workshops, established in 2004 to address semantic disambiguation, role labelling, IE, IR, frame extraction, temporal annotation, and other multilingual semantic processing tasks, adopted our CLEF eHealth data in 2014 [39]. By supplementing our annotations for the CLEF eHealth 2013 tasks 1 and 2, it challenged its participants to the same tasks but on a larger test set. A total of 21 participating teams completed this SemEval 2014 task 1 with the strict-F1 of 81.3% at its best; 18 of those teams also participated in the SemEval 2014 task 2 with the top strict-accuracy of 74.1%. The citation count of this paper was 71 by July 6, 2018.

Limitations

In this paper, we have presented a bibliometric study of the scholarly influence of CLEF eHealth installations from 2012 to 2017. The paper and citation data collection have been limited to the CLEF eHealth proceedings and previously catalogued papers and were conducted only 2 months after the CLEF eHealth 2017 proceedings were published. Consequently, other relevant papers and citations are likely to exist, making our citation influence of 1299 citations in total for the 184 papers by the 741 coauthors from 33 countries a modest rather than exaggerated estimate.

In comparison, the scholarly influence of 6 TREC video retrieval installations from 2002 to 2009 has been evaluated retrospectively 2 years after the last installation as 15,828

citations for the 2073 papers (of which 319 have been published in the TREC conference paper or working note proceedings) [8]. A comparable influence has been achieved within the CLEF initiative by its ImageCLEF activity from 2000 to 2009 [9]. First, 7 ImageCLEF installations were evaluated retrospectively in 2013 (4 years after the 2009 installation) as having had the influence of 2018 citations for the 179 papers. Second, the scholarly influence of 10 installations of the entire CLEF initiative from 2000 to 2009 has been evaluated retrospectively in 2013 (4 years after the 2009 installation) as 9137 for the 873 papers.

Our average number of citations generated by a paper (ie, 7) is smaller than this number is for the entire CLEF initiative (ie, 10) but larger than what many other subinitiatives achieved (from 0.2 to 35, with 11 for ImageCLEF) [9]. CLEF eHealth, established in 2012, is not included in this comparison of 16 CLEF subinitiatives with up to 10 installations each. Moreover, our numbers for 7 installations originate from the year of the last installation as opposed to being collected 4 years after.

Although the CLEF eHealth installations have attracted substantial community interest, as reflected by the 741 coauthors of the 184 papers from 33 countries, we do not really have sufficient participation from Africa, Central and South America, and the Middle East. However, this problem of insufficient participation has been acknowledged by a recent review of evaluation initiatives in biomedical text mining from 2002 to 2014 as one of the main conclusions [40]. Fortunately, we have been successful in targeting the coupled problem of insufficient innovation by reaching statistically significant improvements in most CLEF eHealth tasks.

Significance and Future Work

The CLEF eHealth installations with 15 information management, extraction, and retrieval tasks in total uniquely target various layperson (or next of kin) information understanding and provision challenges in the medical domain (Multimedia Appendix 2). Coupled with this, it strives to drive research in the fields of clinician information processing, exchange, and understanding support. Finally, for the first time globally it targets challenges toward meeting the needs of policy makers for TAR generation in empirical medicine. In IE, the lab has targeted named entity recognition and normalization in clinical reports and named entity recognition, normalization, and classification in biomedical articles and in death reports. In information management, the lab has considered medical data visualization and nurses' handover report management. Finally, in IR the target has been on patient-centered search, cross-lingual search, and technology-assisted reviewing.

The lab has attracted considerable and growing interest from the research community over the years: 34 unique teams participated in the 3 tasks in 2013, 24 in the 3 tasks in 2014, 20 in the 3 tasks in 2015, 20 in the 3 tasks in 2016, and 32 in the 3 tasks in 2017. While the lab has yet to become entirely global, it is already far reaching, attracting participants from 33 countries.

By virtue of the lab series over the first 6 years of its life, from 2012 to 2017 inclusive, we conjecture that CLEF eHealth has

influenced progress by (1) bringing the research community together through the lab series to collaborate and discuss challenges associated with technique development in the biomedical and clinical information management, extraction, and retrieval spaces; (2) providing access to shared data, resources, processing methods, and evaluation settings for eHealth system research, development, and evaluation; and (3) offering reproducibility, scalability, and user-centricity. While it is difficult to accurately quantify such influence, the 1299 citations with influence of circa 963,000 generated by the lab in its first 6 years of existence are suggestive. Progress in the areas addressed by the lab has the potential to generate high impact not only on the research field but more generally on society, given the importance of health information access to support health care as well as empower people to manage their health.

Conclusions

In today's information overloaded society it is increasingly difficult to retrieve and digest valid and relevant electronic medical information to make health-centered decisions. The CLEF eHealth lab aims to support the development of techniques to ease this challenge. Over the years this lab series has expanded its original goal of supporting patients (or their

next of kin) in understanding the jargon in their hospital discharge summary to consider a broader set of medical information needs of both patients (or their next of kin), clinicians, scientists, and policy makers. Related to these themes, challenges have been offered in a multilingual setting on the topics of medical information management, extraction, and retrieval. The 15 challenge tasks, from 2013 to 2017, have attracted much attention, as evidenced by the annual lab overview papers, participants' working notes papers, and external papers using the lab resources, obtaining a combined total of 184 papers by 741 coauthors from 33 countries across the world with 1299 citations, totalling a citation influence of circa 963,000. Given the significance of the lab series, all test collections and resources associated with the lab challenges have been made available to the wider research community through the internet.

The lab has attracted many participants from across the globe since its conception 6 years ago. In total, 718 teams have registered their interest in the lab tasks, leading to 130 teams submitting to these tasks. Together we have influenced the progression of health text processing and medical IR research. As the lab further progresses, we envision its scope and reach extending even further.

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Authors' Contributions

HS, LK, and LG have co-chaired the CLEF eHealth initiative in 2012-2018 and led some of its tasks. In order to review the outcomes of CLEF eHealth, HS first conceptualized the study and then designed and supervised its citation content analysis and review, which the coauthors conducted in close collaboration. HS, LK, and LG drafted the manuscript together, with dedicated sections for each coauthor. After this all authors critically commented and revised the manuscript. All authors have read and approved the final version of the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Electronic health records and other health information.

[[PDF File \(Adobe PDF File\), 808KB - resprot_v7i7e10961_app1.pdf](#)]

Multimedia Appendix 2

Timeline of Conference and Labs of the Evaluation Forum eHealth and related conference proceedings and working notes.

[\[PDF File \(Adobe PDF File\), 767KB - resprot_v7i7e10961_app2.pdf\]](#)

Multimedia Appendix 3

Summary of the bibliometric analysis of Conference and Labs of the Evaluation Forum eHealth from 2013 to 2017.

[\[PDF File \(Adobe PDF File\), 883KB - resprot_v7i7e10961_app3.pdf\]](#)

Multimedia Appendix 4

Summary of the benchmark results for the Conference and Labs of the Evaluation Forum eHealth tasks from 2013 to 2017.

[\[PDF File \(Adobe PDF File\), 895KB - resprot_v7i7e10961_app4.pdf\]](#)

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Abbreviations

CLEF: Conference and Labs of the Evaluation Forum, formerly known as Cross-Language Evaluation Forum

CUI: concept unique identifier
EOI: expression of interest
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
ICT: information and communications technology
IE: information extraction
IR: information retrieval
Khresmoi: Knowledge Helper for Medical and Other Information Users
MeSH: Medical Subject Heading
MIMIC: Multiparameter Intelligent Monitoring in Intensive Care
NDCG@10: normalized discounted cumulative gain at 10
NICTA: National Information and Communications Technology Australia
NLP: natural language processing
P@10: precision at 10
PMID: PubMed identifier
ShARc: shared annotated resources
SNOMED CT: Systematized Nomenclature of Medicine–Clinical Terms
SR: speech recognition
TAR: technology-assisted reviews
TREC: Text Retrieval Conference
UMLS: unified medical language system

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