JMIR Research Protocols

Impact Factor (2022): 1.7
Volume 6 (2017), Issue 6 ISSN 1929-0748 Editor in Chief: Xiaomeng (Simone) Ma, PhDc, MS, BS

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The Effects of Preoperative Volume Replacement in Diabetic Patients Undergoing Coronary Artery Bypass Grafting Surgery: Protocol for a Randomized Controlled Trial (VeRDiCT Trial)

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Abstract

Background: Diabetes mellitus is a major risk factor for prolonged hospital stays, renal failure, and mortality in patients having coronary artery bypass grafting (CABG). Complications pose a serious threat to patients and prolong intensive care and hospital stays. Low glomerular filtration rate (GFR) due to existing renal impairment or volume depletion may exacerbate acute renal impairment/failure in these patients. Preoperative volume replacement therapy (VRT) is reported to increase the GFR and we hypothesize that VRT will reduce renal impairment and related complications in diabetic patients.

Objective: The objective of this study is to establish the efficacy of preoperative VRT in reducing postoperative complications in diabetic patients undergoing CABG surgery. Time to "fit for discharge", incidence of postoperative renal failure, cardiac injury, inflammation, and other health outcomes will be investigated.

Methods: In this open parallel group randomized controlled trial, 170 diabetic patients undergoing elective or urgent CABG surgery received 1 mL/kg/hour of Hartmann's solution for 12 consecutive hours prior to surgery, versus routine care. The primary outcome was time until participants were "fit for discharge", which is defined as presence of: normal temperature, pulse, and respiration; normal oxygen saturation on air; normal bowel function; and physical mobility. Secondary outcomes included: incidence of renal failure; markers of renal function, inflammation, and cardiac damage; operative morbidity; intensive care stay; patient-assessed outcome, including the Coronary Revascularization Outcome Questionnaire; and use of hospital resources.

Results: Recruitment started in July 2010. Enrolment for the study was completed in July 2014. Data analysis commenced in December 2016. Study results will be submitted for publication in the summer of 2017.

Conclusions: VRT is a relatively easy treatment to administer in patients undergoing surgical procedures who are at risk of renal failure. This experimental protocol will increase scientific and clinical knowledge of VRT in diabetic patients undergoing elective or urgent CABG surgery. Findings supporting the efficacy of this intervention could easily be implemented in the health care system.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 02159606; http://www.controlled-trials.com/ISRCTN02159606 (Archived by WebCite at http://www.webcitation.org/6rDkSSkkK)

(JMIR Res Protoc 2017;6(6):e119) doi:10.2196/resprot.7386

KEYWORDS

coronary artery bypass surgery; diabetes mellitus; renal failure; volume replacement therapy; clinical trials; randomized

Introduction

Diabetes mellitus (DM) has been recognized as a major risk factor for atherosclerosis [1,2], and its prevalence is on the rise due to an increasingly aging and obese population [3]. DM is also a major risk factor for postoperative renal failure, infections, and in-hospital and late mortality in patients undergoing coronary artery bypass grafting (CABG) surgery [4,5]. Diabetic patients currently represent approximately 20% of all patients undergoing CABG surgery [3,4,6-8]. This rate does not include undiagnosed DM, which has been reported to be 5.2% of all patients admitted for CABG [6]. In keeping with the United Kingdom (UK) average, approximately 20% of CABG patients have a diagnosis of DM on admission at our institution [4]. However, we have previously demonstrated that only 40% of patients experiencing postoperative moderate-to-poor blood sugar control after CABG were diagnosed as having DM prior to surgery [9]. This finding suggests that the prevalence of undiagnosed DM in patients admitted for CABG may be grossly underestimated, and emphasizes the importance of optimizing the perioperative management of these patients.

Renal insufficiency and acute kidney injury (AKI) remain frequent and serious complications following cardiac surgery, and are associated with other postoperative complications, mortality, prolonged hospital stays, and costs [7-9]. AKI following CABG is also consistently associated with DM [7-9]. Our group has demonstrated that DM is an independent predictor of renal insufficiency in a large cohort study [9], consistent with previous reports linking DM with AKI [8]. AKI can be defined in various ways. The introduction of the Risk, Injury, Failure, Loss, and End stage (RIFLE) criteria have standardized the National Health Service (NHS) definition of AKI and allowed more objective comparisons between different studies [10]. In its most severe form, AKI requires dialysis [10-12]. Death is 7-8 times more frequent in patients requiring dialysis because of AKI [13], but less severe renal dysfunction is also strongly associated with mortality [14]. AKI is reported to be more common after CABG in diabetic patients compared to nondiabetic patients [6,9].

Body fluid volume depletion may also be prevalent in patients undergoing CABG, especially diabetics. One factor leading to volume depletion is preoperative use of diuretics, which can cause hypovolemia, which reduces cardiac preload, cardiac output, and related organ perfusion. In addition, the use of vasodilators can also lead to relative volume depletion and hypotension [15]. Diminished renal perfusion can be a consequence of volume depletion, and of hemodynamic changes associated hypovolemia or with impaired left ventricular function [15,16]. In addition, agents such as nonsteroidal antiinflammatory drugs, cyclosporine, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers can decrease renal perfusion [17-19]. In these situations, the resultant diminution in renal blood flow and estimated glomerular filtration rate (eGFR) can lead to postoperative renal insufficiency, and surgical patients could benefit from mild preoperative fluid replacement therapy since this has been associated with an increase in GFR [20]. A reduced eGFR may simply be a reflection of ongoing baseline renal impairment, which is also typical of diabetic patients.

Isotonic crystalloid solutions, such as Hartmann's solution, are the first choice for volume replacement therapy (VRT) [21]. Unlike plasma expanders, crystalloid solutions have no nephrotoxic (or other specific) side-effects [21]. Isotonic crystalloid solutions are distributed rapidly into the tissue interstitial compartment and have a half-life of 20-30 minutes in the intravascular space.

This study protocol seeks to examine the effects of preoperative gentle VRT on postoperative time to "fitness for discharge", renal failure, inflammation, cardiac injury, postoperative complications, and mortality in diabetic patients undergoing CABG surgery. A definitive trial of VRT in this indication is required before this relatively easy-to-administer treatment can be proposed as adjuvant therapy in diabetic patients undergoing cardiac surgery, or indeed other major surgical procedures. We hypothesize that the postoperative incidence of renal failure will be lower, and postoperative recovery faster, in diabetic patients treated with gentle VRT prior to surgery.

The main objective of the Volume Replacement in Diabetic Patients Undergoing Coronary Artery Bypass Grafting Surgery: Protocol for a Randomized Controlled Trial (VeRDiCT) is to evaluate the effect of VRT versus routine care on time until participants are "fit for discharge", which is defined as normal temperature, pulse, respiratory rate, oxygen saturation on air, bowel function, and physical mobility. Secondary objectives will be to evaluate the effect of VRT versus routine care on the incidence of: postoperative renal failure and biochemical serial markers of renal function, inflammation, and cardiac damage; operative morbidity; intensive care stay; and use of hospital resources. In addition, we will evaluate patient-assessed outcome, which will be based on the serial administration of the Coronary Revascularization Outcome Questionnaire (CROQ).

We are conducting an open, parallel group, randomized controlled trial (RCT) in which diabetic elective or urgent patients undergoing CABG surgery will receive VRT or routine care. This treatment has already been shown to prevent AKI in certain clinical scenarios [21]. The most likely mechanism of action of VRT is by increasing eGFR [20]. It has also been suggested that VRT is essential to obtain adequate systemic circulation and microcirculation [22].

Methods

Type of Clinical Trial

This is an open, parallel group, RCT of preoperative VRT with Hartmann's solution versus routine care in diabetic patients undergoing CABG. The trial is not blinded, as it is not possible to mask the infusion of the Hartmann's solution. A covered drip could have been set up for all trial patients but it would still be

obvious to the patient and those responsible for their care whether or not a fluid infusion was being given.

Study Setting

This study was conducted in Bristol, UK at the Bristol Heart Institute, University Hospital Bristol NHS Foundation Trust. A parallel study was run at Rabindranath Tagore International Institute of Cardiac Sciences (RTIICS), Kolkata, India. The results of both trials are being combined and recruitment at both sites has contributed to the target sample size. RTIICS was responsible for research governance and approvals of their study.

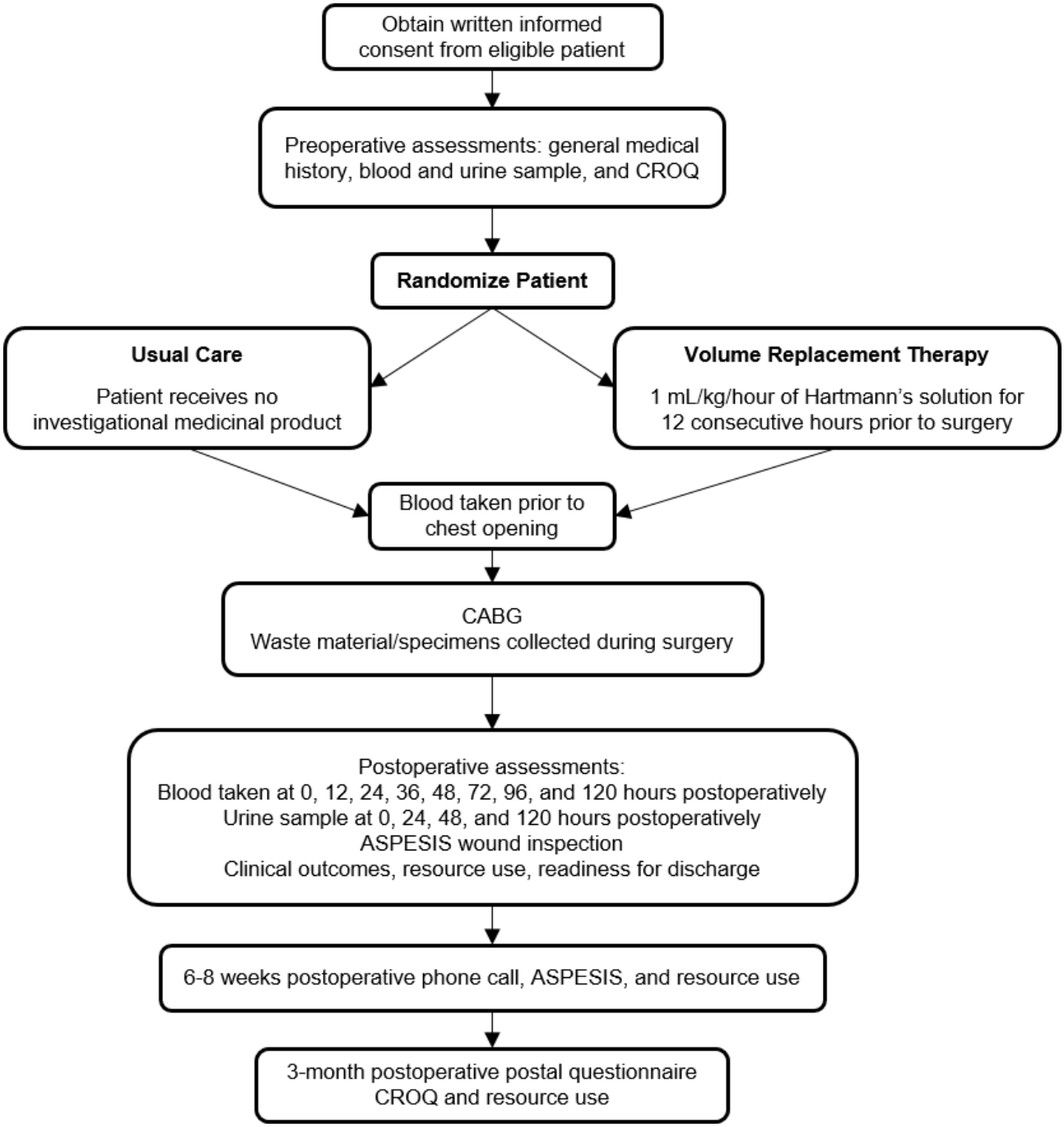
Ethical Review

The University Hospital Bristol NHS Foundation Trust has sponsored the trial in the UK. The trial was approved by the North Somerset & South Bristol Research Ethics Committee (REC; reference 10/H0106/1) in February 2010 in the UK. The study is a Clinical Trial of an Investigational Medicinal Product (IMP) and was approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) in 2010. The study is registered (ISRCTN 02159606).

Participants

For this study, 170 diabetic patients undergoing CABG surgery were recruited to the two parallel studies according to the flow chart shown in Figure 1.

Figure 1. Study flow chart.



Participant Recruitment

To assess eligibility, a member of the local research team (study clinician/research nurse/trial coordinator) in collaboration with the chief investigator (CI) has assessed patients' medical notes to assess eligibility. VRT can be used in most adult diabetic patients for whom CABG is planned. Therefore, all diabetic adults aged >16 years and <80 years having elective or urgent isolated CABG for the first time represented the target study population. Participants could enter the study if all of the following applied: (1) patient was diagnosed with type I or type II diabetes, treated with oral medication and/or insulin (ie, not diet controlled only); (2) aged >16 and <80 years; (3) underwent elective or urgent isolated first-time CABG; (4) left ventricular ejection fraction >30%. Participants were excluded from the study if they had: (1) undergone previous cardiac surgery; (2) emergency or salvage operation; (3) chronic renal failure requiring dialysis; (4) current congestive heart failure; (5) left ventricular ejection fraction <30%.

Information and Consent

Potential trial participants were identified from CABG waiting lists (elective patients) and theatre schedules (urgent patients). All potential participants were sent or given an invitation letter and Patient Information Sheet (PIS) approved by the REC, which described the study. The patient was given time to read the PIS and to discuss their participation with others outside the research team (eg, relatives or friends) if they wished. Most patients had at least 24 hours to consider whether they would participate. In a few cases this time interval was shorter (eg, for patients admitted for urgent surgery without prior notification to the waiting list coordinator). Details of all patients approached for the trial and reason(s) for nonparticipation (eg, reason for being ineligible or patient refusal) were documented. Signed informed consent was required and taken from all eligible patients who were willing to participate.

Study Medication

Hartmann's solution is classed as an IMP and is therefore under the regulation of the MHRA. The IMP was only administered to patients randomized to the VRT arm (there was no placebo). The dosage of the solution is dependent on body mass as follows: 1mL/kg/hour for 12 hours; therefore, maximum dose (mL) = body mass x 12.

Study medication was stored at room temperature in a temperature-monitored lockable cupboard. If the surgery was delayed and rescheduled to take place the next calendar day (morning or afternoon slot), the intervention was not to be repeated. If the surgery was delayed for 2 days or more, the intervention was repeated, and the IMP was represcribed.

Procedure

Patients were randomly assigned in a 1:1 ratio using an Internet-based randomization system (Sealed Envelope Ltd). Cohort minimization was used to achieve balance between groups. Random allocations were generated by computer once the relevant baseline data required to identify the patient and establish eligibility were entered into the system. Consented patients were randomized in the evening on the day of admission, with the VRT intervention delivered overnight prior to surgery. If the operation was unexpectedly rescheduled, the patient retained their study number and randomized allocation. There was no requirement to have code breaking procedures in place. The trial was unblinded and the treatment was recorded in the medical notes and on the fluid chart.

Participants were randomly assigned to receive either VRT (1 mL/kg/hour of Hartmann's solution for 12 consecutive hours prior to surgery) or usual care (no additional preoperative fluids). Both groups were fasted for 6 hours prior to surgery. At surgery, patients were managed according to routine anesthetic, surgical, and perfusion standards. Undertaking of coronary surgery with or without cardiopulmonary bypass and cardioplegic arrest were performed according to the surgeon's preference. All other aspects of the patient's preoperative and postoperative management were in accordance with existing protocols in use. The VRT was the only intervention administered over and above the usual care. Participants were asked to donate small blood and urine samples before, during, and after surgery, as well as any leftover tissue available during surgery that would normally be discarded. At discharge, participants were asked to indicate how they felt about their readiness to go home. At 6-8 weeks postsurgery, participants were asked to complete a telephone assessment of their wounds to ascertain presence of infection and answer a question regarding readmissions. Wounds were assessed using a recognized quantitative scoring method that provides a numerical score related to the severity of wound infection using objective criteria, including additional treatment, serous discharge, erythema, purulent exudate, separation of the deep tissues, isolation of bacteria, and the duration of inpatient stay (ASEPSIS). Three months after surgery, participants were asked to complete the CROQ. Key data collection points are shown in Table 1.

Table 1. Key data collection points of measured outcomes.

	Pre-surgery	Day of surgery	Day 1	Day 2	Day 3	Day 4	Day 5	Discharge	6-8 weeks	3 months
Eligibility	✓									
Written consent	✓									
Randomized allocation	✓									
Demographics and past medical history	✓									
Blood for serum creatinine (AKI/ eGFR) and other biochemical predictors of health outcome	✓	✓ ✓ (0, 12 hours)	✓ ✓ (24, 36 hours)	✓	✓	✓	✓			
Operative details		✓								
Clinical outcomes								✓		
CROQ	✓									✓
Readiness for discharge								✓		
ASEPSIS wound inspection					✓		✓	✓		
ASEPSIS post-discharge surveillance									✓	
Resource use data								✓	✓	✓
Urine sample (renal glomerular and tubular injury, microRNA and other biochemical predictors of health outcome)	✓	✓	✓	✓			✓			
Blood for fasting glucose and hemoglobin A1c	✓ (prior to chest opening)									
Blood for serum and plasma microRNA	✓	✓	✓				✓			
Leftover material/specimens collected during surgery		✓ (intra-operatively)								
Blood for Troponin T	✓	✓ ✓ (0, 12 hours)	✓	✓	✓		✓			
Blood for C-reactive protein	✓	✓ ✓ (0, 12 hours)	✓	✓	✓		✓			

Results

Primary Outcome

The primary outcome is the time until patients are classified as "fit for discharge", since prevention of renal impairment by the proposed intervention is expected to impact the risk of many postoperative complications. A patient must have normal temperature, pulse, respiratory rate, oxygen saturation on air, and bowel function and be physically mobile (taking into account preoperative mobility such as wheel chair use) in order to be classified as "fit for discharge".

Secondary Outcomes

Secondary outcome measures include: (1) measurements of serum creatinine from blood samples collected preoperatively and postoperatively; (2) microalbumin/creatinine ratio measured in urine samples collected preoperatively and postoperatively; (3) N-acetyl-beta-D-glucosaminidase release measured in urine samples collected preoperatively and postoperatively; (4) participants' judgement about readiness for discharge; (5)

in-hospital mortality and morbidity; (6) use of health care resources; (7) health-related quality of life as measured by the CROQ; (8) preoperative fasting blood glucose; (9) micro-ribonucleic acid (RNA) measured in preoperative and postoperative urine, serum, and plasma samples; (10) C-reactive protein (CRP) measured preoperatively and postoperatively; and (11) serial troponin T release measured preoperatively and postoperatively. Measures 8-11 were only included in a subgroup of the UK trial.

Safety Reporting

Side Effects

No previous randomized trials of VRT during cardiac surgery have been carried out, or were ongoing, at the time of the study. Hartmann's solution is widely used for VRT, and is not known to cause allergic reactions or hemodynamic instability in this patient group. In this study, the solution was given at a very slow rate to have minimal impact on the well-being of the patient preoperatively. The solution was administered via a peripheral line that the patient would always have inserted at some point during their admission, so this was not considered to pose any additional risk.

Withdrawal of Individual Participants

Participants could withdraw from the study at any time for any reason and without any sanction. Researchers, after consulting with the CI and the study coordinator, could also interrupt the treatment program if, in their opinion, continuing the treatment may affect the patient's welfare.

Suspension of the Study

In cases of suspected severe adverse events related to the administration of the treatment, the study could be interrupted and the researchers and coordinator would decide whether to continue.

Reporting of Adverse Events

Adverse events were recorded from the randomization time point, throughout the duration of the participant's postoperative hospital stay, and for the predefined 3-month follow-up period. Any adverse event spontaneously reported by the participant, or observed by the researcher or the research team, was be recorded on the case report form (CRF) that was designed for this purpose. Events were also reported in accordance with the International Conference for Harmonization of Good Clinical Practice guidelines and followed the sponsor's policy for safety reporting. Expected events included those related to administering Hartmann's solution, as well as complications associated with cardiac surgery.

Anticipated Benefits

Potential benefits to participants include the possibility of improved renal protection for the intervention group, which we hypothesize will lead to a reduced incidence of postoperative renal insufficiency and a faster postoperative recovery. Should our hypothesis be supported by the findings of the trial, all future diabetic patients undergoing CABG should benefit from preoperative volume replacement. The main benefit to society is the provision of high quality evidence to address this important area of clinical uncertainty.

Data Analysis

Sample Size

There were no previous trials of VRT in diabetics, hence no data to guide the likely target difference in renal function to be observed for the purpose of sample size calculation. No published data existed for the primary outcome of "fit for discharge" (chosen to minimize biases that can affect standard data on postoperative length of stay) and the sample size calculation described here uses information about actual postoperative length of stay as a proxy for the primary outcome. The median postoperative stay for diabetic patients having CABG (from our institutional database) is 7 days. Assuming time to "fit for discharge" is shorter than actual stay, we have proposed that the trial should be able to detect a 25% difference in the proportion of patients "fit for discharge" at 6 days between VRT and usual care groups (ie, 75% vs 50%). We have proposed that 170 participants would be required to detect this target difference with 90% power and 5% significance (2-tailed).

Statistical Analyses

Time to "fit for discharge" and length of Intensive Care Unit and postoperative hospital stays will be analyzed as time-to-event data using regression modelling for survival data. Means for continuous outcomes (transformed logarithmically if required) will be compared using regression modelling, adjusting for baseline covariates where available; "mixed models" will be used for outcomes with repeated measures such as eGFR and markers of glomerular, tubular, renal function, microRNA, CRP, and troponin T. Findings will be reported as effect sizes with 95% confidence intervals. The frequencies of complications and conversions will be tabulated descriptively. Analyses will be based on the intention-to-treat (as treated compared to intention-to-treat); conversions are expected to be rare.

A subgroup analysis comparing trial-specific (eg, UK or India) primary and secondary biochemical marker outcomes is prespecified in the statistical analysis plan. Subgroups will be compared by adding an allocation by trial interaction term into the model.

Trial Status

Of the 491 patients assessed for eligibility during the study period, 169 patients (120 in UK, 49 in India) were successfully recruited and randomized over a 48-month period. Study recruitment was closed in July 2014. Study results are expected to be published in the summer of 2017.

Discussion

Principal Findings

The VeRDiCT study offers a unique opportunity to answer a fundamental question about a clinical intervention, which could reduce postoperative complications in an increasing proportion of atherosclerotic diabetic patients. To the best of our knowledge, at the time of study design there were no other

ongoing trials investigating the clinical benefit of VRT in diabetic patients undergoing coronary surgery. To investigate the potential clinical efficacy of VRT, it is necessary to undertake a well-designed RCT to assess the impact of VRT on renal function and health outcomes in the selected patient cohort. The proposed research should contribute significantly to the understanding of the role of VRT in reducing postoperative complications in diabetic patients undergoing surgery and, if successful, contribute significantly to improving health care while reducing the burden on hospital resources. A multi-dimensional methodological approach based on the evaluation of an extensive list of objective and serial clinical, biochemical, and functional measures should prove valuable in characterizing the effects of VRT. Studying serial biochemical markers of renal and cardiac injury (and of inflammatory activation) at baseline, during surgery, and postoperatively might provide evidence for an organ-specific impact of VRT, which in turn should translate into health outcome benefits. In particular, a reduction in renal failure should affect the primary outcome of time to "fitness for discharge". The methods used in this trial to assess renal, myocardial, and inflammatory function and activation have traditionally been employed in cardiac surgery and in diabetic patients [2-5,9].

Following discussion during the study design period, it was decided that the trial was not going to be blinded, as it was not practically possible to mask the infusion of the Hartmann's solution. A covered drip could have been set up for all trial patients but it would have still been obvious to the patient and those responsible for their care whether or not a fluid infusion was being given. In addition, the prescription would have been visible in the medical record. However, the outcome endpoints of the trial are based on objective measures, hence the influence of the lack of blinding is minimal.

In undertaking this trial, the study team have encountered a number of logistical problems that reflect the difficulty of conducting research within a routine setting. The first was the variability of the information supplied to our institution (a tertiary referral center for cardiac surgery) upon referral of the patient. This variable made it difficult to establish which patients were diabetic, and this delay reduced the time available to approach the patient about the study, and for the patient to consider their participation. This issue was particularly problematic for urgent inpatients transferred directly from another hospital, often with very short notice. In these latter cases, this problem also had an impact on delivery of the intervention. The study was further hampered by the introduction of a *Day of Surgery Admission* (DOSA) policy implemented during the recruitment phase. The DOSA policy imposed a system by which elective patients would be preadmitted for a few hours for baseline evaluations two weeks before surgery, and were no longer admitted the evening before surgery, but on the morning of surgery. Patients admitted as DOSA could not be given the intervention, as there was not enough time to administer the 12-hour infusion of VRT. The study team was able to work with the waiting list coordinators to admit potential trial patients the night before surgery, but pressure on beds meant that this was not always possible.

The trial was conceived in Bristol, UK. The study design and protocol were discussed and agreed between the two trial teams following a preparatory visit to Kolkata by the UK CI. To enhance consistency across the trials, the Indian trial used the same protocol, study documents, and CRFs as the UK team. The Indian trial also used Sealed Envelope Ltd for randomization.

During the recruitment phase, there were two amendments to the study protocol. The first one consisted of removing the fixed 12-hour cap that allowed the patient to consider entering the trial; this was done to allow the inclusion of urgent inpatients referred at short notice from other hospitals. Inclusion of these patients is important to ensure that study results are generalizable to the study population that is likely to benefit from the intervention. Patients were only consented if they felt that they had had enough time to consider their participation. A second amendment (for a sub-cohort of patients) consisted of expanding the list of outcome measures, including a measure of baseline fasting glucose, an extra time point for sampling of blood and urine, and inclusion of microRNA, CRP, and troponin I as extra biochemical markers.

Limitations

This is the first trial assessing the efficacy of preoperative VRT in diabetic patients undergoing coronary surgery on postoperative renal function and health outcomes. There are, however, some potential limitations: (1) only one dose of VRT was administered; (2) only the elective and urgent patient population was studied; and (3) logistical difficulties, such as the introduction of the DOSA policy, meant that patients otherwise eligible were not included. Future investigations should seek to determine the effects of higher doses of VRT, and doses that are administered during the postoperative period in these patients.

Acknowledgments

The VeRDiCT trial was funded by a Garfield Weston Trust (GWT) grant (PMS/MMS - 07/08-3001) to Professor Ascione. The study was also supported by the National Institute for Health Research (NIHR) Bristol Cardiovascular Biomedical Research Unit, the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol, and by the British Heart Foundation (BHF). The views expressed in this publication are those of the authors and not necessarily those of the GWT, the NHS, the NIHR, the Department of Health, or the BHF. The study is sponsored by the University Hospitals Bristol NHS Foundation Trust. The authors would like to thank all study team members involved in the recruitment, coordination, and data collection for this trial, as well as the surgeons who contributed surgical patients at both participating centers.

Authors' Contributions

MC coordinated the data validation and team meetings during the last year, and helped with the draft of the manuscript. TH coordinated the trial during the intermediate period. CR helped in securing the funding, advised on the study design, undertook the sample size calculation, and oversaw the statistical analyses. LC oversaw management of the trial and helped to draft the manuscript. JT helped to set up the trial in Bristol and coordinated it during the initial phase. GDA helped in securing the funding. PN coordinated the trial in India and performed some of the operations. BR helped in securing the funding and advised on the study design. JH helped with study design. KA helped with trial coordination. KS was the site-specific lead for the Indian center and performed most of the surgery at this site. RA was the Chief Investigator on this trial, conceived the trial, secured the finding, designed the study, set up the collaboration with the Indian center, performed most of the surgery at the UK center, and drafted the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AKI: acute kidney injury
ASEPSIS: additional treatment, serous discharge, erythema, purulent exudate, separation of the deep tissues, isolation of bacteria, and the duration of inpatient stay
BHF: British Heart Foundation
CABG: coronary artery bypass graft
CI: chief investigator
CRF: case report form
CROQ: Coronary Revascularization Outcome Questionnaire
CRP: C-reactive protein
DM: diabetes mellitus
DOSA: Day of Surgery Admission
eGFR: estimated glomerular filtration rate
GFR: glomerular filtration rate
GWT: Garfield Weston Trust
IMP: Investigational Medicinal Product
MHRA: Medicines and Healthcare Products Regulatory Agency
NHS: National Health Service
NIHR: National Institute for Health Research
PIS: Patient Information Sheet
RCT: randomized controlled trial
RIFLE: Risk, Injury, Failure, Loss, and End stage
RNA: ribonucleic acid
RTIICS: Rabindranath Tagore International Institute of Cardiac Sciences
REC: Research Ethics Committee
UK: United Kingdom
VeRDiCT: Volume Replacement in Diabetic Patients Undergoing Coronary Artery Bypass Grafting Surgery: Protocol for a Randomized Controlled Trial
VRT: Volume Replacement Therapy

Edited by G Eysenbach; submitted 23.01.17; peer-reviewed by HY Choi; comments to author 20.03.17; revised version received 13.04.17; accepted 14.04.17; published 19.06.17.

Please cite as:
Clout M, Harris T, Rogers C, Culliford L, Taylor J, Angelini G, Narayan P, Reeves B, Hillier J, Ashton K, Sarkar K, Ascione R
The Effects of Preoperative Volume Replacement in Diabetic Patients Undergoing Coronary Artery Bypass Grafting Surgery: Protocol for a Randomized Controlled Trial (VeRDiCT Trial)
JMIR Res Protoc 2017;6(6):e119
URL: http://www.researchprotocols.org/2017/6/e119/
doi:10.2196/resprot.7386
PMID:28630035

Protocol

A Hybrid Web-Based and In-Person Self-Management Intervention to Prevent Acute to Chronic Pain Transition After Major Lower Extremity Trauma (iPACT-E-Trauma): Protocol for a Pilot Single-Blind Randomized Controlled Trial

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Abstract

Background: Acute pain frequently transitions to chronic pain after major lower extremity trauma (ET). Several modifiable psychological risk and protective factors have been found to contribute to, or prevent, chronic pain development. Some empirical evidence has shown that interventions, including cognitive and behavioral strategies that promote pain self-management, could prevent chronic pain. However, the efficacy of such interventions has never been demonstrated in ET patients. We have designed a self-management intervention to prevent acute to chronic pain transition after major lower extremity trauma (iPACT-E-Trauma).

Objective: This pilot randomized controlled trial (RCT) aims to evaluate the feasibility and research methods of the intervention, as well as the potential effects of iPACT-E-Trauma, on pain intensity and pain interference with daily activities.

Methods: A 2-arm single-blind pilot RCT will be conducted. Participants will receive the iPACT-E-Trauma intervention (experimental group) or an educational pamphlet (control group) combined with usual care. Data will be collected at baseline, during iPACT-E-Trauma delivery, as well as at 3 and 6 months post-injury. Primary outcomes are pain intensity and pain interference with daily living activities at 6 months post-injury. Secondary outcomes are pain self-efficacy, pain acceptance, pain catastrophizing, pain-related fear, anxiety and depression symptoms, health care service utilization, and return to work.

Results: Fifty-three patients were recruited at the time of manuscript preparation. Comprehensive data analyses will be initiated in July 2017. Study results are expected to be available in 2018.

Conclusions: Chronic pain is an important problem after major lower ET. However, no preventive intervention has yet been successfully proven in these patients. This study will focus on developing a feasible intervention to prevent acute to chronic pain transition in the context of ET. Findings will allow for the refinement of iPACT-E-Trauma and methodological parameters in prevision of a full-scale multi-site RCT.

Trial Registration: International Standard Randomized Controlled Trial Number (ISRCTN): 91987302; http://www.controlled-trials.com/ISRCTN91987302 (Archived by WebCite at http://www.webcitation.org/6rR8G2vMs)

(JMIR Res Protoc 2017;6(6):e125) doi:10.2196/resprot.7949

KEYWORDS

acute pain; chronic pain; risk factors; protective factors; self-management; early intervention; cognitive therapy; Internet; wound and injuries; lower extremity; feasibility studies; pilot projects

Introduction

Acute to Chronic Pain Transition After Major Extremity Trauma

Approximately 65% of traumatic injuries occur in individuals aged 18 to 55 years [1], compromising their most productive years of life. Orthopedic lesions, including lower extremity trauma (ET), affect the majority of injured individuals (80%) [1]. More than 50% of patients with major ET (ie, patients at risk of impaired outcomes usually requiring surgical and multidisciplinary team management) report moderate to severe pain at hospital discharge [2,3], which becomes chronic in up to 86% of cases [4,5]. Pain has several negative consequences. Indeed, poorly managed acute pain has been associated with undesirable outcomes, such as delayed recovery and prolonged length of hospital stay [6,7]. Moreover, intense acute pain has been identified as a chronic pain risk factor after traumatic injury [4,5].

Acute pain is of sudden onset and is expected to last a short time, and can usually be clearly related to a specific event, injury, or illness [8], such as major ET. Chronic pain is defined as ongoing or intermittent, lasting beyond the injury healing process (or more than 3 to 6 months), and adversely impacts daily functioning as well as quality of life (QoL) [9,10]. Healing time after lower ET varies according to the extent of osseous and soft-tissue damage, patient characteristics (eg, age, smoking history, nutritional deficiency), and quality of surgical treatments [11,12], but does not usually exceed 3 months in the absence of complications [11].

People with chronic pain report poorer QoL than individuals affected by common chronic diseases of the heart and lungs [13], making it the most frequent reason for seeking medical attention [14]. Up to 60% of active people who live with chronic pain (including those with lower ET) will experience pain interference with daily living activities, which can lead to job loss or reduced professional responsibilities [15]. Chronic pain also imposes a high socioeconomic burden, which has been estimated to be US $635 billion annually in terms of health care costs and lost productivity [16,17]. Given the impact of chronic pain, the Institute of Medicine (IOM) of the National Academies [8] made “pain prevention” the highest priority for pain relief. To do so, the IOM called for the early promotion of patient self-management behaviors and consideration of biological and psychosocial factors to prevent acute to chronic pain transition.

Factors Involved in the Development of Chronic Pain

Many longitudinal studies have described chronic pain risk factors. Demographics (eg, female gender, age >65 years, low socioeconomic status) have been shown to play a role in the transition from acute to chronic pain in patients with major ET [4,5]. Moderate to severe acute pain (ie, >4/10 on a numerical rating scale [NRS]) [18] and lower limb trauma are injury-related chronic pain risk factors consistently described in trauma patients [4]. Several potentially modifiable psychological risk factors also seem to be involved, including pain catastrophizing, pain-related fear (ie, kinesiophobia), anxiety, depression, and post-traumatic stress disorder (PTSD) [4,5,19]. However, some patients do not develop chronic pain after ET or other types of injuries, and protective factors have been explored [20,21]. Pain self-efficacy (SE) has been discussed as a protective psychological attribute in acute and chronic pain post-ET [4,22,23]. Pain acceptance has also been associated with improved outcomes in populations that do not include ET patients [24-27].

Interventions to Prevent Acute to Chronic Pain Transition

Interventions based on a cognitive-behavioral approach have been the most frequently-studied [28] treatments addressing potentially-modifiable psychological factors in the context of chronic pain [29]. These interventions are aimed at promoting individual self-management behaviors (eg, skills to control pain and their effects on physical and psychological functioning) when experiencing pain episodes [30,31]. Such objectives are reached through educational, cognitive (ie, prevention or alteration of maladaptive thoughts, problem-solving) and behavioral (ie, relaxation skills, activity pacing, return to pre-injury activities) strategies as well as complementary approaches, such as support (eg, continued monitoring, encouragement) and relapse prevention (eg, self-monitoring and matching of learned self-management behaviors with real-life situations) [32].

A recent systematic review [29] of psychological therapies for chronic pain management concluded that interventions including such strategies were the most effective. Findings revealed small effect sizes (ie, standardized mean difference [SMD] of 0.15 to 0.29) on pain and related disability and moderate effect sizes (SMD of 0.3 to 0.59) on mood and pain catastrophizing compared to standard care or waiting list. However, these tested interventions have been found to have only small positive effects on pain-related disability and pain catastrophizing compared to active controls (ie, physiotherapy, education, or medical regimens). Most of these effects were observed post-treatment but were not maintained at follow-up (ie, 6 to 12 months after treatment).

Considering the refractoriness of chronic pain to treatment, interest has been growing in the development of interventions intended to promote self-management behaviors before acute

pain becomes chronic [28]. Some empirical evidence has revealed that interventions could prevent acute to chronic pain transition several months post-injury, mainly in back pain patients [33-43]. However, no such interventions have been tested in patients with major ET.

In this regard, most randomized controlled trials (RCTs) on preventive self-management interventions have been conducted in patients with pain duration varying from 15 days to 3 months, who were treated in primary care settings or hospital outpatient clinics [33-35,37-43]. The main objective in most of these studies was to restore functioning in activities of daily living and work, and to reduce pain intensity. Most interventions included four to six weekly sessions, which lasted 20 minutes to 2 hours, and were delivered face-to-face individually or in-group. Two to four face-to-face booster sessions to promote the sustainability of intervention effects and/or follow-up phone calls were provided in some studies from two weeks to three months after intervention completion [33,40,42]. Psychologists, nurses, and physiotherapists have most frequently provided these interventions. Research on the effects of such interventions reported positive findings related to pain intensity, restoration of daily functioning, social impact, and psychological variables. Indeed, statistically and clinically significant reductions (between 30% to 50% from baseline) of mean pain intensity scores were observed at 3 and 6 months after the onset of acute pain, favoring the group receiving self-management interventions compared to active controls (ie, education, physiotherapy, biofeedback) [34,41]. Similarly, a study in which participants were classified as back pain "recovered" or "chronic back pain" (based on pain intensity and disability cutoff scores) demonstrated that the number of participants who recovered from their back pain was more than twice as high in the group completing a 4-session self-management program compared to the attention control group (54% vs 23%, P=.02) at 6 months [42].

Positive outcomes on work status were also demonstrated in other RCTs documenting that control group participants, receiving usual care or education through written document, were at a 3-to-9-fold greater risk of long-term sick leave (ie, a total of 15-30 or more days in the past 6 months) compared to those receiving the self-management intervention [37-39]. Similarly, patients at risk of chronic back pain showed significant decreases in health care service utilization (ie, self-reported number of visits to physicians or physiotherapists) or were less often referred to multidisciplinary programs for pain at 1-year follow-up when they had received a self-management intervention, in comparison to those who had not.

Furthermore, research findings have shown that the early implementation of self-management interventions designed to increase the patients' abilities to respond to pain in a more adaptive way contributed to better psychological outcomes. For example, participants who received such interventions demonstrated more positive attitudes towards back pain self-care abilities and significant reductions in pain worry and kinesiophobia at 1-year follow-up [41,43] compared to participants who received education only. Another study showed that participants who received a self-management intervention exhibited less maladaptive behaviors (eg, self-blame) and more adaptive behaviors (eg, problem-focused) [36]. In this regard, experimental group participants were less depressed than the control group subjects, who were 7 times more likely to develop psychopathologies (ie, anxiety, sleep and somatoform disorders) at 1-year follow-up.

Based on knowledge acquired from positive outcomes associated with early self-management programs, we have designed a self-management intervention to prevent acute to chronic pain transition after major lower extremity trauma (iPACT-E-Trauma). Specifically, the intervention focuses on reducing pain intensity and pain interference with daily living activities, to maintain scores <4/10, as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for chronic pain prevention [44]. Patients with an injury to a lower extremity have clinical conditions, recovery profiles, and continuum of care that are different from patients with back pain, necessitating the development of an intervention that fits their specific needs. For example, ET injuries and movement limitations immediately after trauma require the administration of targeted pharmacological and nonpharmacological strategies (ie, cryotherapy, legs being elevated) to reduce inflammation and acute pain in the first intervention sessions, instead of focusing on restoring function. Moreover, ET patients are hospitalized in acute care settings before being transferred to an inpatient and/or outpatient rehabilitation center. The ET patients' capacity to participate in self-management intervention while in these settings must be considered when selecting the intervention's dose (ie, duration and number of sessions) and delivery modes. Similarly, the evolving ability of ET patients to bear weight on their injured limb must be considered when guiding them in their return to previous activities, and in the application of pain management strategies (eg, restarting the use of analgesics and cryotherapy for a few days when initially bearing weight on the injured limb).

Empirical and clinical data have guided the development of a preliminary version of the iPACT-E-Trauma intervention, which was refined after the assessment of its acceptability by clinicians (nurses, orthopaedic surgeons, a family physician specialized in pain management, a psychiatrist and physiotherapists) and patients (unpublished observations; Bérubé, Gélinas, Martorella, Feeley, Côté, Laflamme, Rouleau, Choinière; under review). Clinicians and patients positively evaluated the acceptability of the preliminary version of iPACT-E-Trauma. To further improve the suitability (ie, how easy the intervention is applied in the context of daily life) and convenience (ie, willingness to participate in the intervention) [45] of the iPACT-E-Trauma intervention, procedures for the documentation of self-management behaviors by patients were simplified, and session durations were reduced (ie, 15 minutes instead than 30 minutes) as recommended by clinicians. Acceptability assessment of the iPACT-E-Trauma intervention by patients allowed for the tailoring of iPACT-E-Trauma key features based on determinants such as pain intensity, previous knowledge, and the application of self-management behaviors. Furthermore, based on clinicians' and patients' input, a Web application was developed to facilitate the intervention delivery in acute care

settings. In this paper, an RCT protocol is described to pilot test the refined iPACT-E-Trauma intervention, which is required before evaluating its efficacy in a full-scale multi-site RCT.

Objectives

Primary Objectives

We aim to evaluate intervention and research method feasibility, as well as iPACT-E-Trauma preliminary effects on pain intensity and pain interference (co-primary outcomes) with daily living activities at 6 months post-injury.

Secondary Objectives

We aim to: (1) explore the preliminary effects of iPACT-E-Trauma intervention on patients' perceived pain SE, pain acceptance, pain catastrophizing, pain-related fear, anxiety and depression symptoms, health care service utilization, and return to work (secondary outcomes) at 6 months post-injury; and (2) examine patients' acceptability assessment of iPACT-E-Trauma [45].

Hypotheses

We hypothesize that the experimental group will experience a clinically significant reduction of pain intensity (ie, >2 points on a 0-10 NRS) [46] and pain interference with daily living activities (ie, >1 point on a 0-10 NRS) [46] compared to the control group at 6 months post-injury. We expect that the participants in the experimental group will also present higher rates of *no pain* or *mild pain* intensity and/or pain interference scores (ie, <4/10) [44] on these two outcomes. Secondly, we hypothesize that the experimental group will present increased pain SE and pain acceptance as well as reduced pain catastrophizing, pain-related fear, anxiety and depression symptoms, health care service utilization, and increased return to work compared to the control group at 6 months post-injury.

Trial Design

A 2-arm single-blind pilot RCT will be used. Participants will be randomized to either an experimental group (iPACT-E-Trauma intervention and usual care) or control group (educational pamphlet and usual care) and followed according to the study time points (T1 to T8) presented in Figure 1. The Standard Protocol Items on Recommendations for Interventional Trials (SPIRIT) will be followed [47], per the checklist presented in Multimedia Appendix 1.

Methods

Setting

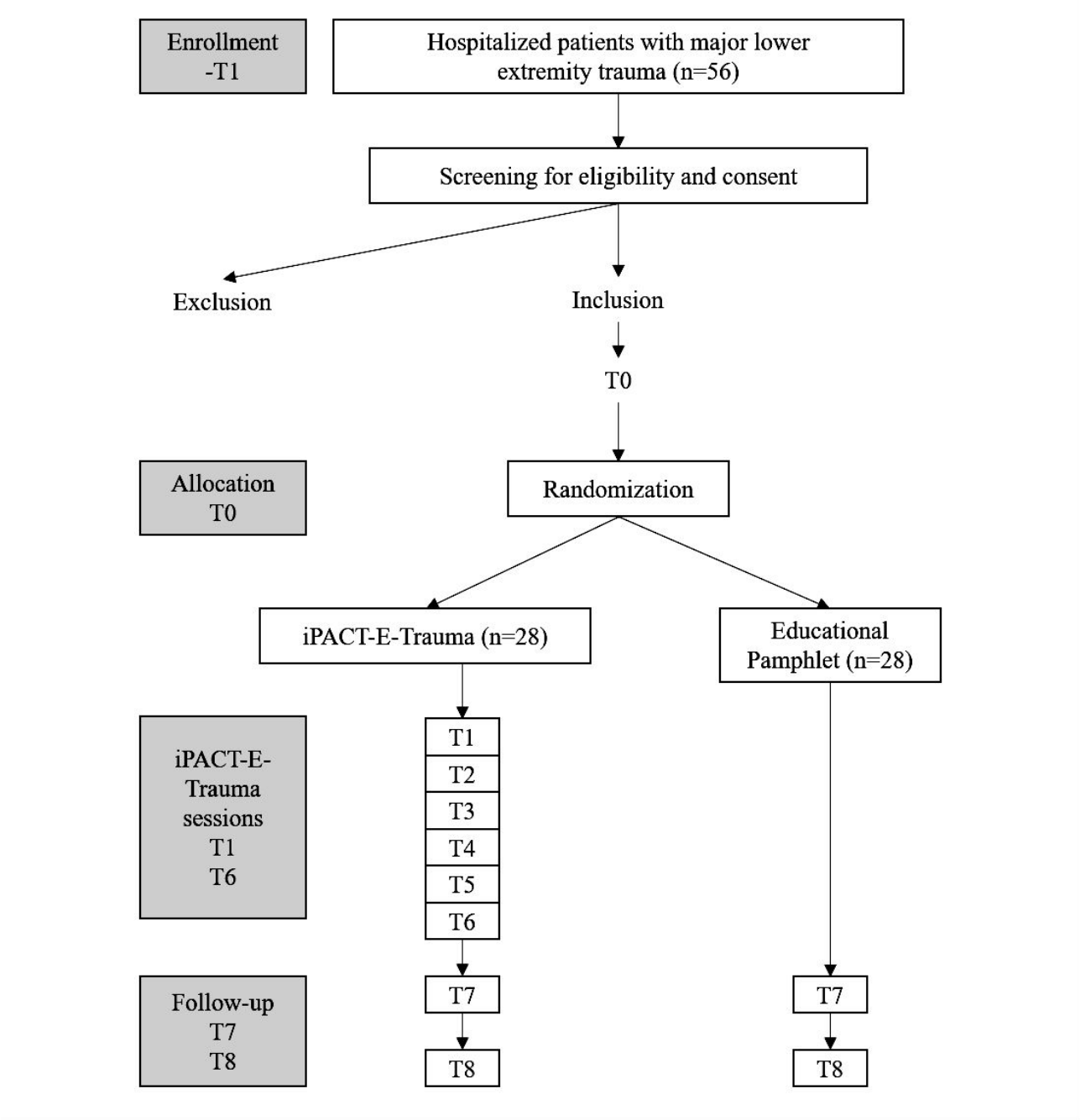
The study will be conducted in a level-1 academic trauma center in Montreal, Canada. The intervention will be provided to the experimental group during their hospitalization in the level-1 trauma center and after hospital discharge. The control group will receive an educational pamphlet while in the trauma center.

Eligibility Criteria

The inclusion criteria will be: (1) age 18 years or older; (2) able to read and speak French; (3) have a major ET; and (4) at risk of developing chronic pain. Several chronic pain risk factors have been identified in patients with major ET, with acute pain intensity found consistently in this population. IMMPACT has recommended the consideration of this inclusion criterion in chronic pain prevention studies [44]. Patients will be enrolled if they present pain intensity >4/10 upon movement 24 hours post-injury. Waiting 24 hours post-injury to enroll patients will allow their pain intensity to be adequately documented, and will allow us to determine if they are at risk of chronic pain before the administration of the intervention. Considering that lower ET has been identified as a chronic pain risk factor (and to optimize sample homogeneity) only patients with such injuries will be recruited.

The exclusion criteria among ET patients will be: (1) spinal cord injury; (2) other trauma associated with high-intensity pain (eg, >2 rib fractures [48] or surgical abdominal trauma [18]) or principal site of pain not being lower ET; (3) amputation; (4) cognitive impairment (eg, dementia, severe psychiatric disorder, Glasgow Coma Scale score <13/15) [49]; and (5) >7 days of hospitalization. This last criterion was established to minimize delays in intervention delivery, and to standardize intervention timing. Since traumatic injuries occur more frequently in older adults [50], pre-injury somatic pain (eg, pain caused by joint osteoarthritis) will not be an exclusion criterion unless patients report daily analgesic use prior to the trauma. Likewise, patients with a history of visceral pain (eg, inflammatory bowel disease) will not be excluded, considering that this type of pain can be differentiated from musculoskeletal pain caused by a lower ET. Although substance abuse may influence the intervention's outcomes, this comorbid factor will not be an exclusion criterion. The prevalence of alcohol abuse in patients who have sustained a traumatic injury ranges from 40% to 70% [51-53] and could reach 33% for drug abuse [54]. Excluding patients with a history of substance abuse would impact the external validity of the study. However, data on substance abuse will be collected at baseline and its potential effects on outcomes will be analyzed separately to explain findings, and to inform the research methods of a future full-scale RCT (eg, need for stratified randomization to control for the confounding factor).

Figure 1. Flow diagram showing the flow of patients in the study protocol.



Intervention

Control Group

Participants randomized to the control group will receive standard pain management interventions consisting of analgesic administration (ie, opioids and co-analgesia such as acetaminophen and pregabalin) by nurses, according to standardized medical pre-printed orders, and physiotherapy sessions. To ensure that iPACT-E-Trauma effects will not be based exclusively on information and attention patients receive, an educational pamphlet will be distributed to control group participants. The pamphlet will be administered by the research nurse >24 hours (but within 7 days) after hospital admission. The research nurse will visit participants the day after educational pamphlet distribution to answer their questions. Participants will be free to seek medical or other professional care for pain management after hospital discharge.

Experimental Group

Participants in the experimental group will receive iPACT-E-Trauma as well as standard pain management interventions. These individuals will be free to seek other pain management treatments after hospital discharge. The biopsychosocial model of chronic pain and empirical data guided the development of the iPACT-E-Trauma intervention; more specifically its ultimate and immediate goals, components, activities, delivery modes, and dose [55].

Intervention Content

The biopsychosocial model of chronic pain [56] emphasizes the fact that physical disorders, such as pain, result from

dynamic interactions between biological, psychological, and social factors, which may perpetuate and worsen pain. The psychological dimension of the model includes cognitive, affective, and somatic factors, which were taken into account when developing the intervention. *Cognitive factors* refer to promoting pain SE and pain acceptance while minimizing pain catastrophizing and pain-related fear. *Affective factors* relate to emotional reactions, such as anxiety and depression symptoms. It is expected that the intervention's effects on cognition and affect will influence *somatic factors* by supporting patients in their development of adaptive responses (ie, self-management behaviors) to acute pain, thereby reducing the biologically-related dimension (ie, pain intensity). The development of self-management behaviors and the reduction of pain intensity may then positively influence pain interference with daily living activities, health care service utilization, and return to work, which relate to the social dimension of the biopsychosocial model of chronic pain.

The ultimate goal of iPACT-E-Trauma corresponds to the primary objective of this study, which is to reduce pain intensity and pain interference with daily living activities (co-primary outcomes). Immediate goals relate to determinants that should be changed to manage acute pain and pain interference with daily living activities (ie, to increase pain SE and pain acceptance, and to decrease pain catastrophizing, pain-related fear, and anxiety and depression symptoms [secondary outcomes]). To reach these goals, iPACT-E-Trauma focuses on the following components: (1) the biopsychosocial dimensions of pain and the prevention/regulation of maladaptive thoughts, emotions, and behaviors; (2) the optimal use of pharmacological strategies for acute pain management; (3) the optimal use of nonpharmacological strategies for acute pain management (ie, cryotherapy, leg elevation, relaxation exercises); (4) the adoption of health-promotion strategies (ie, staying active and maintaining an adequate sleep routine); and (5) the return to pre-injury activities. Specific components of iPACT-E-Trauma correspond to several strategies found in cognitive-behavioral interventions (ie, education, problem-solving, activity pacing, graded activity, continued monitoring, encouragement, and matching of learned self-management behaviors with real-life situations). These strategies will be tailored throughout intervention sessions according to the participants' pain experience, previous knowledge, and adherence to suggested self-management behaviors.

Intervention Structure

The iPACT-E-Trauma intervention combines five individual 15-to-30-minute online, face-to-face, and telephone sessions delivered by a nurse starting 24 hours after hospital admission (or after surgery, when required). The intervention also includes two face-to-face or telephone-based booster sessions lasting 15-to-20 in minutes duration. The nurse who will deliver the intervention has received training to deliver the intervention based on a cognitive-behavioral approach (Progressive Goals Attainment [57]). Previous self-management interventions aimed at preventing chronic pain have been delivered individually or to groups, and both strategies have been associated with positive outcomes. Although no such intervention has been provided online or by telephone, these modes were incorporated into iPACT-E-Trauma to facilitate its delivery and to reach patients after hospital discharge. A recent meta-analysis revealed positive results about the delivery of interventions based on a cognitive-behavioral approach in patients with various chronic pain conditions via the Internet alone, or combined with live interactions with clinicians [58]. Telephone-based self-management interventions have shown effects comparable to those in face-to-face interventions in the context of chronic pain [59,60].

According to the intervention dose, most preventive self-management interventions analyzed in the literature review included a total of 4 to 8 weekly sessions of 20 minutes to 2 hours in duration [33,35-39,41,43]. Two to four face-to-face booster sessions were most commonly provided from 2 weeks to 3 months after intervention completion [33,40,42]. A meta-analysis of effective delivery doses in the context of pain supports this time duration [61], since better empirical evidence has been obtained for interventions lasting less than 8 weeks compared to interventions lasting more than 8 weeks. Shorter interventions may improve attendance, give greater learning opportunities, and increase the potential to motivate and engage participants [61].

The iPACT-E-Trauma intervention includes seven short-length sessions to facilitate their integration shortly after injury (Table 1). The first three sessions are planned to be delivered via the Web with the *Traitement et Assistance Virtuelle Infirmière et Enseignement* (TAVIE) platform [62] (ie, *Soulage TAVIE Post-Trauma*) and will be combined with a face-to-face mode of delivery during patient hospitalization. More specifically, participants will be invited to watch a virtual session, followed by a short visit by a research nurse the day after, to answer questions and reinforce learned self-management strategies. Session 2 will be given two days after session 1, and session 3 will be given one week after session 1. The two other regular sessions (ie, sessions 4 and 5) will be delivered on a weekly basis face-to-face during hospitalization or patient appointment in the orthopedic outpatient clinic for medical follow-up, or by telephone if it is not possible to meet the patient in person. Two booster sessions (ie, sessions 6 and 7) will be given by telephone or at the orthopedic outpatient clinic at 6 weeks and 3 months post-injury.

Table 1. iPACT-E-Trauma Sessions.

Session	Delivery Timing	Components
1. Web combined with in-person at the hospital	>24 hours to 7 days post hospital admission	Biopsychosocial dimensions of pain: introduction to the biopsychosocial dimensions of pain and how they negatively or positively influence the pain experience
		Self-assessment of pain intensity
		Nonpharmacological pain management/cryotherapy and elevation of legs
2. Web combined with in-person at the hospital	Two days after the first session	Follow-up on previously learned self-management behaviors based on an assessment of patient's need (ie, pain intensity and adherence to proposed self-management behaviors)
		Pharmacological pain management strategies: analgesics and co-analgesia
		Nonpharmacological pain management strategies/relaxation exercises with a focus on deep breathing relaxation
3. Web combined with in-person at the hospital	One week after the first session	Follow-up on previously learned self-management behaviors based on an assessment of patient's need
		Biopsychosocial dimensions of pain: prevention/regulation of maladaptive thoughts, emotions and behaviors
		Health promotion/strategies for staying active in the presence of persistent pain: part 1
4. In-person at the hospital or by telephone	One week after the third session	Follow-up on previously learned self-management behaviors based on an assessment of patient's need
		Health promotion strategies/sleep hygiene
		Health promotion/strategies for staying active in the presence of persistent pain: part 2
5. In-person at the hospital or by telephone	One week after the fourth session	Follow-up on previously learned self-management behaviors based on an assessment of patient's need
		Pharmacological pain management strategies: how to gradually reduce the consumption of analgesics
		Return to pre-injury activities: establishment of an action plan for returning to pre-injury activities
6. Booster 1: in-person at the hospital or by telephone	Two weeks after the fifth session	Review of the previously learned self-management behaviors if pain intensity >4/10 and/or pain interfering with daily activities on a regular basis
		Pharmacological pain management strategies: how to gradually reduce the consumption of analgesics
		Revision of the plan for returning to pre-injury activities
7. Booster 2: in-person at the hospital or by telephone	Four weeks after the first booster session (3 months post-injury)	Review of the previously learned self-management behaviors if pain intensity >4/10 and/or pain interfering with activities on a regular basis
		Pharmacological pain management strategies: how to gradually reduce the consumption of analgesics
		Referral to appropriate resources if the patient is still experiencing pain intensity >4/10 and taking opioids on a regular basis
		Revision of the plan for returning to pre-injury activities

Variables and Measurement Tools

A number of variables will be measured at different time points (Multimedia Appendix 2) to meet study objectives based on the SPIRIT statement [47]. Complementary variables will be evaluated to facilitate data interpretation and comparison with other populations.

Feasibility

An Intervention Feasibility Evaluation Logbook and Self-Management Behavior Assessment Checklist will allow for the documentation of intervention feasibility data (Multimedia Appendix 3) [55]. The Intervention Feasibility Evaluation Logbook will detail information on intervention components that need to be delivered in each session, the number of webpages and documents consulted on the *Soulage TAVIE Post-Trauma* platform, the appropriateness of the physical environment in which the intervention is delivered, the time dedicated by participants to watch Web sessions, the time required to deliver in-presence sessions by the nurse, and challenges faced in providing the intervention [63]. The Self-Management Behavior Assessment Checklist will allow for the documentation of participants' engagement and

adherence to the intervention (ie, participation in intervention activities and application of recommended self-management behaviors) [63]. A Research Methods Feasibility Form will assess essential criteria of methodological research parameters (Multimedia Appendix 3) [55,64]: (1) adequacy of the sampling pool and recruitment time, (2) ease with which participants are screened, (3) possibility of applying randomization procedures as planned, (4) attrition rate in experimental and control groups, and (5) ease of data collection procedures.

Primary and Secondary Outcomes

A comprehensive set of outcome measures will be recorded 24 hours to 7 days post-injury (baseline) and 3 and 6 months later (follow-up). The Brief Pain Inventory (BPI) will measure both primary outcomes (ie, pain intensity and pain interference with daily living activities). Secondary outcomes will be quantified through validated questionnaires: the Pain Self-Efficacy Questionnaire (PSEQ), the Chronic Pain Acceptance Questionnaire-8 items (CPAQ-8), the Pain Catastrophizing Scale (PCS), the Tampa Scale for Kinesiophobia (TSK), and the Hospital Anxiety and Depression Scale (HADS). Health care service utilization will be measured via a Medical Attention Seeking and Professional Services Utilization Logbook, and return to work will be measured with a form that documents work status and responsibility modifications at work. In addition, the Patient Global Impression of Change (PGIC) scale will assess perceived improvement [46]. All instruments have been translated into French using a forward-backward method and/or cultural adaptation. All French version instruments have shown adequate psychometric properties [65-71] as detailed in Multimedia Appendix 4.

Brief Pain Inventory

The BPI includes 11 items: 4 on pain intensity (now, average, worst, least) measured on a 0-10 NRS (0=no pain; 10=worst possible pain), and 7 on pain interference with daily living activities, assessed on a 0-10 NRS (0=does not interfere; 10=interferes completely) [72]. The BPI item “walking” was replaced by “mobility (ability to get around)” as proposed in a study performed in persons with cerebral palsy [73] because many patients with major ET may be limited in their walking capacity. Moreover, three additional items (pain interference with self-care, recreational activities, and social activities), proposed in a modified version of the BPI [73], will be added to the Pain Interference with Daily Living Activities Subscale to obtain a broader-based sample of areas that could potentially be affected by pain. Pain intensity upon movement on average in the last 7 days, and total score of pain interference with daily living activities during the same period, will serve as primary outcome measures. Baseline measures of pain intensity and interference will cover the previous 24 hours.

Pain Self-Efficacy Questionnaire

PSEQ is a 10-item questionnaire, which assesses the confidence that people with ongoing pain have in their abilities to manage pain and perform activities while in pain [74]. PSEQ scores range from 0 to 49; scores <17 represent very low SE while scores >40 indicate the likely maintenance of behavioral changes, which is the aim of increasing pain SE [74].

Chronic Pain Acceptance Questionnaire-8 Items

CPAQ-8 is an 8-item questionnaire measuring pain acceptance. This scale comprises two subscales: the degree to which patients engage in daily living activities regardless of pain (4 items), and the willingness to experience pain (4 items) [75]. No information on relevant score changes has been found.

Pain Catastrophizing Scale

PCS comprises 13 items divided into three subscales (rumination, magnification, and helplessness) measuring catastrophizing thoughts [76,77]. Total PCS scores range from 0 to 52; a score of 30 represents a clinically-relevant level of catastrophizing [77].

Tampa Scale for Kinesiophobia

TSK is a 17-item checklist developed as a measure of fear of movement/(re)injury in the context of pain [78]. Total score ranges between 17 and 68, with 37 and above differentiating between high and low scores [79].

Hospital Anxiety and Depression Scale

HADS is a 14-item inventory divided into two subscales, each comprising 7 items to assess anxiety (HADS-A) and depression (HADS-D) [80]. The range of each subscale is 0-21. Cut-off scores for both subscales indicate that 0-7=normal, 8-10=mild anxiety/depression, 11-14=moderate anxiety/depression, and 15-21=severe anxiety/depression.

Patient Global Impression of Change

PGIC [81,82] is a core outcome measure that allows participants to rate their overall improvement regarding their: (1) pain, (2) functioning level, (3) QoL, and (4) global condition [83,84], on a 4-point Likert scale (considerably improved; considerably deteriorated).

Acceptability

Two questionnaires will assess intervention acceptability: (1) an E-Health Acceptability Questionnaire that integrates recommended features of Internet-based interventions [85] for Web sessions, and (2) an Intervention Acceptability Questionnaire for in-presence sessions [45]. The E-Health Acceptability Questionnaire has been developed to analyze TAVIE platform content [85], and includes 21 items evaluated on a 5-point descriptive scale, which is divided into 9 subscales: ease of use, ease of understanding, credibility, tailoring, relevance, applicability, visual design appreciation, dosage, motivational appeal, and overall satisfaction with the Internet-based intervention. Experts in the field established content validation of this questionnaire [85].

The Intervention Acceptability Questionnaire is based on a validated instrument intended to describe respondents’ evaluation of intervention acceptability (Treatment Acceptability and Preference Questionnaire: TAP) [45]. The specific acceptability attributes included in this questionnaire are: (1) effectiveness in managing the problem, (2) intervention appropriateness, (3) suitability of the intervention to individual reality, and (4) convenience or willingness to apply and adhere to the intervention. TAP reliability was established in a population receiving behavioral interventions for insomnia

(Cronbach alpha >0.80) [45]. Validity was confirmed through factor analysis, confirming 1-factor structure and discriminant validation. TAP has been adapted to evaluate the acceptability of intervention components and activities in this study. Open-ended questions have been added after each item to obtain participants' input on required modifications to render the intervention more acceptable.

Complementary Variables

Short Form 12 items, Version 2

The Short Form 12 items, version 2 (SF-12v2) is a 12-item general measure of health status, facilitating comparisons of outcomes among different disorders and treatments [82]. This scale comprises 8 subscales: physical functioning, role limitation due to physical health problems, bodily pain, general health, vitality, social functioning, emotional health problems, and mental health [86,87]. The scales can be aggregated to provide Physical Component Summary scores and Mental Component Summary scores [88]. SF-12v2 utilizes a linear T-score transformation method so that scores for each of the health domains and component summary measures have a mean of 50 and standard deviation of 10. Scores above and below 50 are above and below the average. Items of the SF-12v2 have been translated into French by a Canadian research team using a forward-backward method, quality ratings of the translated product, and reevaluation of items, as well as pilot testing [89].

Injuries and Treatments

An Injury Profile Form will describe injury-related aspects that may affect patients' pain intensity and recovery. The following aspects will be documented: mechanisms of injury, number of fracture(s), open fracture(s) and their grade, other injuries (eg, mild traumatic brain injury), injury severity score [90], type of treatments received (surgical and nonsurgical), number of surgeries required, soft-tissue injuries, access to compensation, pre-injury chronic pain, substance abuse, technical aids to facilitate ambulation, and fracture healing status.

Analgesics Consumption

The Analgesics Consumption Form will describe the analgesics taken by participants during their hospitalization in the trauma center, referring regional hospital, and/or rehabilitation center. After patients are discharged to go home, the number of pills of each analgesic taken will be documented every week. Analgesic consumption will be measured until 6 weeks post-injury, since this timeline has been associated with greater consumption of analgesics after major ET [91].

Douleur Neuropathique 4

This 10-item questionnaire documents the presence of neuropathic pain [92], which is a type of pain that is more complex to treat than somatic pain [93]. A score >4 suggests neuropathic pain.

Pcl-5

PCL-5 is a 20-item self-report measure that assesses 20 Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) PTSD symptoms [94]. Although iPACT-E-Trauma does not aim to treat PTSD, PCL-5 will be administered, since PTSD has been identified as a risk factor for chronic pain post-ET. PCL-5 has been shown to be reliable (Cronbach alpha=0.94; test-retest reliability r=0.82) and valid (convergent r=0.74-0.85; discriminant r=0.31-0.60; confirmed DSM-5 4-factor model) [94]. Scores range from 0 to 80, and a cut-point of 33 establishes the presence of PTSD [95]. The psychometric properties of the French version have not yet been tested.

Sample Size

The sample size of a pilot trial should provide reasonable confidence to guide investigators in their decisions about proceeding to a larger trial. Sample sizes that are too large should be avoided due to costs and ethical issues. An 80% 1-sided confidence interval of estimated main trial effect size has been proposed to achieve such aims [96]. Chronic pain prevention studies are not informative about the effect size that should be used to calculate pilot trial sample size. Hence, the effect size documented in chronic pain trials (SMD=0.25-0.35 [29,58]) regarding pain intensity and pain interference with daily activities (primary variables) was used to calculate sample size, and was estimated to be 23 participants per group [96]. With prevision of a 20% attrition rate often encountered in longitudinal studies [64], a total of 56 participants will be recruited and randomized into each group (experimental and control).

Recruitment

Nurses, medical residents, orthopedic surgeons, and an orthopedic trauma case manager nurse will identify possible participants, inform them about the study, and obtain their permission to be contacted by the principal investigator (PI; MB). These professionals have been informed about the study's inclusion-exclusion criteria during information sessions. The name and medical file number of patients giving permission to be contacted will be provided to the PI by those who are referring participants via verbal communication or confidential voicemail messages. The PI will then visit these patients. If patients meet the inclusion criteria and wish to participate after receiving a full explanation of the study, the PI will obtain their written informed consent (Multimedia Appendix 5).

Allocation

Randomization

The randomization sequence will be generated by a coordinating center to keep researchers blinded. A computerized random-number generator will produce the sequence. Randomization will be undertaken in permuted blocks of 4 to decrease allocation predictability. Tickets will be placed in sealed, opaque, sequentially numbered envelopes to randomize study participants to either the control or experimental group. Participants will be randomized after obtaining baseline data.

Blinding

The research nurse who will administer the intervention cannot be blinded to group assignment considering that she will deliver the iPACT-E-Trauma sessions. To ensure participant blinding to group assignment, the intervention will be delivered (and the educational pamphlet will be distributed) to participants in private hospital rooms, or in hospital rooms in which no other patients are hospitalized for major ET. The research assistant

(RA) who will enter data will be blinded to group assignment. A numerical code will be assigned to each participant in the two groups to allow for statistician blinding.

Data Collection

Procedure

At enrollment, the research nurse delivering the intervention will complete the Injury Profile Form and Research Methods Feasibility Form. She will distribute Sociodemographic and Outcome questionnaires to participants. Questionnaires will be placed in sealed envelopes by participants upon completion, to keep the research nurse blinded to the data. An RA will document analgesics given and services received from rehabilitation professionals before patient enrollment.

During intervention delivery, the research nurse will complete the Self-Management Application Checklist to document the rate of self-management behaviors applied in relation to each intervention session. The research nurse will record information concerning intervention delivery and attrition via the Intervention Feasibility Evaluation Logbook and the Research Methods Feasibility Data Form. An RA will fill out the Daily Analgesics Consumption Form while participants are hospitalized. The medical file of participants transferred to referring regional hospitals or rehabilitation centers will be obtained to complete data on analgesic consumption. After discharge to home, an RA will contact patients' pharmacists to inquire about analgesic distribution. Adequate use of analgesics is a self-management behavior taught within the intervention, so the research nurse will question participants assigned to the experimental group about the remaining quantity of pills in their containers at the beginning of each session, and an RA will phone participants assigned to the control group to question them at corresponding session timelines. A nurse working in the outpatient orthopedic clinic will examine patients for the presence of neuropathic pain by Douleur Neuropathique 4 at each patient's follow-up appointments. Participants will be invited to fill out the Medical Attention Seeking and Professional Services Utilization Logbook until the conclusion of the study.

Participants in the experimental group will have to complete acceptability questionnaires in the week following sessions 3, 5, and 7. Both groups will also have to complete outcome measures (the SF-12v2 and PCL-5) at 3 and 6 months post-injury. Participants will have the choice of completing questionnaires in hard copy or online (ie, SurveyMonkey). If participants select the hard copy format, acceptability questionnaires will be sent to them by mail and packages of the instruments will be provided to them at medical follow-up appointments in the outpatient orthopedic clinic. Should participants be still hospitalized in a regional hospital or rehabilitation center at the time of completing acceptability questionnaires, an RA will administer them over the phone. Instructions will be provided to participants in the experimental and control groups to return a copy of the Medical Attention Seeking and Professional Services Utilization Logbook at 3 and 6 months. If participants prefer to complete the questionnaires online, an email (including the link for questionnaire access) will be sent to them in the week preceding the 3-month and 6-month data collection points. Phone calls or email reminder(s) by an RA will follow twice, with a 1-week interval if the questionnaires are not completed on time.

Data Management

An RA will verify that all questionnaires have been completed at baseline and when they are returned. The RA will hold discussions with participants upon questionnaire completion soon after baseline time point measurement, and contact them by phone at data collection points, to find out why data are missing. If missing data are a result of participant inattention or not understanding a question, the RA will clarify any issues they may have and ask them to provide the missing data. Steps taken to deal with missing data will be noted in the Research Methods Feasibility Data Form.

Data Analysis

Feasibility

To determine the feasibility of iPACT-E-Trauma, rates of planned actions that are applied during interactions with patients, as well as the number of webpages and online documents consulted, will be obtained. Mean time spent by participants watching Web sessions and mean time required for the delivery of intervention sessions by nurses will be computed. Rates of participants' engagement in intervention sessions and in recommended activities, as well as applied recommended self-management behaviors, will also be calculated. Descriptive data pertaining to intervention delivery challenges will be grouped into categories. Frequencies will be calculated for each category.

Regarding Research Methods Feasibility, descriptive data will be obtained to document: (1) the number of eligible patients and number of participants included; (2) the frequency of recruitment approaches; (3) the mean time required to screen participants relative to their recruitment, consent, and baseline data collection; (4) the percentage of patients who accept to be randomized to either the experimental or control group; (5) the dropout rate relative to each intervention session and outcome measure time points; and (6) the attrition rate at study end [55]. Descriptive data from notes written about difficulties experienced during screening procedures, and obtaining consent and baseline data from patients, will be analyzed by regrouping main difficulties into categories. Frequencies will be calculated for each category. The frequency of unmet inclusion and exclusion criteria will be calculated. If >50% of ET patients are deemed ineligible, the reasons for ineligibility will be analyzed and inclusion/exclusion criteria will be reviewed during the present study, and for the full-scale RCT [55]. Frequency counts on the number of questionnaires not completed in time will be obtained. Mean time between expected dates for questionnaire completion and actual completion will be calculated. Recall rates for questionnaire completion will also be computed.

Preliminary Efficacy of the Intervention

All outcome data will be analyzed via an intent-to-treat approach (ie, analyses including all patients randomized, even if they drop out or otherwise have missing data). To estimate differences in primary and secondary variables between the intervention and control groups, a 2-group mixed linear model

design with repeated measures on 1 factor (time) will be applied. This model will allow for the detection of significant group differences in continuous outcomes over time due to the intervention. Moreover, the model incorporates the full-information maximum likelihood (FIML) procedure for handling missing data commonly occurring in repeated-measures designs. FIML allows parameter estimation and measures standard errors of parameter estimates, which are statistically nonbiased processes [97,98]. Differences between the experimental and control groups will be analyzed at baseline, 3 months (ie, at the end of intervention), and at 6 months. The results obtained at 6 months will estimate sample size in prevision of a full-scale multi-site RCT.

Acceptability

Descriptive analyses of acceptability questionnaire data will be conducted. Frequencies will be calculated for each acceptability attribute. Answers to open-ended questions about required modifications to render the intervention more acceptable in terms of effectiveness, appropriateness, suitability and convenience will be grouped into categories for each session.

Ethical Considerations

Procedures have been implemented to ensure that the information participants provide in this study will be kept confidential. All participants will be assigned a unique code number. Consent forms will be stored separately from the data. A master list matching the names of participants with their study identification numbers will be kept in a locked filing cabinet separate from the data. No names or other identifying information will appear in any data that is generated.

Study findings will be presented in comprehensive form and not linked to specific participants. All hard copies of the data will be stored in a locked filing cabinet in a locked office. Online survey software secured with enhanced login and encryption features will safeguard the electronic questionnaire format. Data from electronic questionnaires will be downloaded onto a password-protected computer hard-drive and onto a safety code-protected Universal Serial Bus key. Data will be deleted from online survey software at the conclusion of the study, but will be stored for 10 years and then destroyed, and treated as confidential waste.

Protocol amendments will be communicated to the Institutional Review Board (IRB) and through additional information in the trial registration form. Finally, the intervention is not known to be associated with any adverse events. However, such events will be documented if they emerge throughout the study.

Results

Fifty-three patients were recruited at the time of manuscript preparation. Comprehensive data analyses will be initiated in July 2017. Study results are expected to be available in 2018.

Discussion

Study Contributions

The aims of this pilot RCT are to evaluate the feasibility and research methods of a chronic pain preventive intervention. Testing the intervention will provide information on its preliminary efficacy while allowing more data to be gathered on its acceptability from the perspective of patients. Chronic pain has repeatedly been identified as an important health problem in patients with major ET, but no intervention has yet been proposed for them. Evidence from such interventions in other populations is scarce. Indeed, a great deal of attention has been devoted to the implementation of interventions when pain has already become chronic, but few studies have focused on its prevention. This RCT could allow for the development of an evidence-based intervention tailored to ET patients' needs early after injury.

Preliminary testing of the intervention will set the stage for a full RCT, should the results be promising. If a full RCT shows that the intervention is effective, it will provide professionals of multidisciplinary teams working in the trauma-orthopedics field with scientific guidance and a meaningful way in which to address acute to chronic pain transition. The development of self-management behaviors that decrease long-term reliance on the health care system corresponds to current trends put forward by health policies and health organization decision-makers (ie, to empower patients to take responsibility for their own health and make services more efficient) [8]. A feasible and acceptable intervention aimed at preventing chronic pain could ultimately achieve such objectives while helping to reduce the number of patients with major ET disability and associated social costs.

Study Limitations

Participation burden is an important limitation of this study. Participants in both groups will be asked to complete numerous questionnaires over a long period of time and participants in the experimental group will also have to attend several intervention sessions. To minimize the risk of attrition related to participation burden, patients will be contacted several times throughout the study by phone or email to complete or remind them to complete questionnaires, which will help maximize continued participation. Participants will receive monetary compensation proportional to the number of outcome questionnaire packages completed and intervention sessions attended (ie, Can $10 per questionnaire package and intervention session). The proposed initial number of participants to be recruited accounts for attrition rates commonly reported in longitudinal studies.

A second limitation pertains to the potential generation of social desirability bias since participants will self-report their performance of intervention activities and self-management behaviors. To minimize this type of bias, participants will be informed that honest answers to questions are crucial for developing interventions that will correspond to ET patients' needs, and determine if such interventions should be offered to patients with major ET in the future.

Trial Status

The trial was ongoing at the time of the protocol submission. No comprehensive data analyses had begun at the time of this manuscript preparation.

Ethical Approval and Consent to Participate

IRB approval was obtained from the *Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de Montréal -Hôpital du Sacré-Cœur de Montréal (HSCM)* in June 2016 (HSCM Project No. 2017-1333; Multimedia Appendix 6). The PI will obtain written informed consent from participants before initiating the study.

Acknowledgments

The first author (MB) has received fellowships from the Canadian Institutes of Health Research (MFE-140934), *Fonds de recherche du Québec-Santé* (FRQ-S; 30244) and *Réseau de recherche en sciences infirmières du Québec (* no reference number was provided) to conduct this doctoral research project. The authors received a grant from the Quebec Pain Research Network of FRQ-S (no reference number was provided) for the development of *Soulage Tavie Post-Trauma* and preliminary testing in Web sessions.

We thank Dr. Michel Malo (orthopedic surgeon), Dr. Rahel Giorghis (psychiatrist), Mark Ware (family physician), Sylvie Desjardins, Nathalie Mezzeta, Manon Robidoux, Amélie Fleury-Larocque, and Isabel Roy (nurses) as well as Genevieve Beauchamp-Vien and Nathalie Boutin (physiotherapists) for clinical advice during iPACT-E-Trauma development and study proposal preparation. We also express our gratitude to Patricia Auger and Geneviève Rouleau who provided clinical and technical support during the development of the Web application *Soulage Tavie Post-Trauma*.

Authors' Contributions

MB conceived the protocol in the context of her doctoral studies and drafted the manuscript. CG closely supervised study design and was involved in manuscript drafting. GM, JC, NF, and MC provided clinical and methodological advice regarding the research proposal and critically revised the manuscript. GYL and DR identified clinical data to be measured, and data that will be required for patients' longitudinal follow-up. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

SPIRIT Checklist.

[PDF File (Adobe PDF File), 61KB - resprot_v6i6e125_app1.pdf]

Multimedia Appendix 2

Schedule of enrollment, intervention, and assessments.

[PDF File (Adobe PDF File), 37KB - resprot_v6i6e125_app2.pdf]

Multimedia Appendix 3

Assessment variables for intervention and research methods feasibility.

[PDF File (Adobe PDF File), 79KB - resprot_v6i6e125_app3.pdf]

Multimedia Appendix 4

Psychometric properties of the French version of measurement instruments.

[PDF File (Adobe PDF File), 21KB - resprot_v6i6e125_app4.pdf]

Multimedia Appendix 5

Information and consent form.

[PDF File (Adobe PDF File), 80KB - resprot_v6i6e125_app5.pdf]

Multimedia Appendix 6

IRB approval (original document in French).

[PDF File (Adobe PDF File), 234KB - resprot_v6i6e125_app6.pdf]

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Abbreviations

BPI: Brief Pain Inventory
CPAQ-8: Chronic Pain Acceptance Questionnaire-8 items
DSM-5: Diagnostic and Statistical Manual of Mental Disorders version 5
ET: extremity trauma
FIML: full-information maximum likelihood
FRQ-S: Fonds de recherche du Québec-Santé
HADS: Hospital Anxiety and Depression Scale
HSCM: Hôpital du Sacré-Cœur de Montréal
IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IOM: Institute of Medicine
iPACT-E-Trauma: intervention to prevent acute to chronic pain transition after major lower extremity trauma
IRB: Institutional Review Board
NRS: Numerical Rating Scale
PCS: Pain Catastrophizing Scale
PGIC: Patient Global Impression of Change
PI: principal investigator
PSEQ: Pain Self-Efficacy Questionnaire
PTSD: post-traumatic stress disorder
QoL: quality of life
RA: research assistant
RCT: randomized controlled trial
SE: self-efficacy
SF-12v2: Short Form 12 items, version 2
SMD: standardized mean difference
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAP: Treatment Acceptability and Preference Questionnaire
TAVIE: Traitement et Assistance Virtuelle Infirmière et Enseignement
TSK: Tampa Scale for Kinesiophobia

Edited by G Eysenbach; submitted 30.04.17; peer-reviewed by S Sidani, I Gilron; comments to author 10.05.17; revised version received 17.05.17; accepted 23.05.17; published 26.06.17.

Please cite as:
Bérubé M, Gélinas C, Martorella G, Côté J, Feeley N, Laflamme GY, Rouleau D, Choinière M
A Hybrid Web-Based and In-Person Self-Management Intervention to Prevent Acute to Chronic Pain Transition After Major Lower Extremity Trauma (iPACT-E-Trauma): Protocol for a Pilot Single-Blind Randomized Controlled Trial
JMIR Res Protoc 2017;6(6):e125
URL: http://www.researchprotocols.org/2017/6/e125/
doi:10.2196/resprot.7949
PMID:28652226

Protocol

Mobile Phone Short Messages to Improve Exclusive Breastfeeding and Reduce Adverse Infant Feeding Practices: Protocol for a Randomized Controlled Trial in Yangon, Myanmar

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Abstract

Background: Myanmar has a high burden of mortality for children aged younger than 5 years in which undernutrition plays a major role. Despite current efforts, the exclusive breastfeeding rate for children under 6 months is only 24%. To date there have been no interventions using mobile phones to improve breastfeeding and other feeding practices in Myanmar.

Objective: This study aims to implement a breastfeeding promotion intervention using mobile phone text messages in Yangon, Myanmar, and evaluate its impact on breastfeeding practices.

Methods: M528 is a 2-group parallel-arm randomized controlled trial with 9 months follow-up from recruitment until 6 months post-delivery. A total of 353 pregnant women between 28 and 34 weeks' gestation who had access to a mobile phone and were able to read and write have been recruited from the Central Women's Hospital, Yangon, and allocated randomly to an intervention or control group in a 1:1 ratio. The intervention group received breastfeeding promotional SMS messages 3 times a week while the control group received maternal and child health care messages (excluding breastfeeding-related messages) once a week. The SMS messages were tailored for the women's stage of gestation or the child's age. A formative qualitative study was conducted prior to the trial to inform the study design and text message content. We hypothesize that the exclusive breastfeeding rate in the intervention group will be double that in the control group. The primary outcome is exclusive breastfeeding from birth to 6 months and secondary outcomes are median durations of exclusive breastfeeding and other infant feeding practices. Both primary and secondary outcomes were assessed by monthly phone calls at 1 to 6 months postdelivery in both groups. Participants' delivery status was tracked through text messages, phone calls, and hospital records, and delivery characteristics were assessed 1 month after delivery. Child morbidity and breastfeeding self-efficacy scores were assessed at 1, 3, and 5 months postdelivery. Social desirability was measured at 5 months, and text messages expressing delivery success and user experience were assessed at the end of the study.

Results: The targeted 353 pregnant women were recruited between January and March 2015. Baseline data have been collected; SMS messages have been developed and pretested and sent to the women from both groups. Follow-up data collection via phone calls has been completed. Data analysis is being done and results are expected soon. This is the first RCT study examining the effects of mobile text messaging for promoting exclusive breastfeeding.

Conclusions: This trial is timely in Myanmar following the telecommunications market opening in 2014. Our results will help determine whether text messaging is an effective and feasible method for promoting appropriate feeding practices and will inform further research to assess how this model could be replicated in the broader community.

Trial Registration: Australian New Zealand Clinical Trial Registry ACTRN12615000063516; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367704 (Archived by WebCite at http://www.webcitation.org/6rGif3l81)

(JMIR Res Protoc 2017;6(6):e126) doi:10.2196/resprot.7679

KEYWORDS

randomized controlled trial; mHealth; text messaging (SMS); intervention studies; exclusive breastfeeding; infant and young child feeding; nutrition; Myanmar; pregnant women; child health

Introduction

Globally, undernutrition is the underlying cause of an estimated 45% of deaths in young children and contributes to 35% of the disease burden in children under 5 years and 11% of total global disability-adjusted life years [1-3]. Myanmar is facing undernutrition as a public health problem, with 23% of children under 5 years of age being underweight and 35% stunted [4], which exceeds the global average of 25% [5]. Myanmar also has a high under-5 child mortality rate of 46 deaths per 1000 live births [4]. The Global Strategy for Infant and Young Child Feeding recommends that newborns should start breastfeeding within 1 hour after birth and that infants should be exclusively breastfed for the first 6 months and for an additional 18 months or longer with appropriate complementary food [6]. The benefits of breastfeeding are well documented, and breastfeeding promotion programs are a cost-effective public health measure to prevent the leading causes of child mortality such as diarrhea, pneumonia, and neonatal sepsis [7-11]. The 2013 Lancet series on maternal and child nutrition and a study in Nepal highlighted that high coverage of community-based early breastfeeding initiation and exclusive breastfeeding (EBF) promotion programs could prevent an estimated 13% of under-5 deaths and almost 20% of neonatal deaths [12-14].

In Myanmar, regardless of race or religion, breastmilk is considered the most beneficial food for newborns, and breastfeeding is culturally and socially supported in both urban and rural areas [15]. Our recent formative qualitative study showed that expectant mothers traditionally believe the benefits of breastmilk and husbands and family members support breastfeeding. However, if women have insufficient milk or have to return to work, formula milk was favored by those who could afford it due to the stereotype of affordability or influence of advertising, while poor women would provide cow or goat's milk and sweetened condensed milk mixed with warm water or milk powder [16]. The latest national survey conducted in Myanmar reported that 90% of mothers were aware of the benefits of breastmilk and 76% fed breastmilk to their newborn within 1 hour after birth, but only 24% of infants less than 6 months of age were exclusively breastfed [4]. This EBF rate is the second lowest in the World Health Organization (WHO) South-East Asia Region after Thailand [17].

Globally, with increased availability of mobile phones, the use of mobile technology for health-related interventions (mHealth) has greatly increased [18,19]. Several maternal and child health nutrition promotional studies have used mobile text messages to disseminate educational information to a target audience. A Text4baby study in the United States reported that exposure to short message service (SMS) or text messages was associated with belief changes in pregnant women [20], and a recent meta-analysis of mHealth interventions for maternal, newborn, and child health in low- and middle-income countries found high levels of impact for EBF [21]. An Australian study conducted with 234 mothers showed that women who received breastfeeding promotional text messages had a slower decrease in EBF (6% per month) compared to the women receiving usual care, who had a 14% decrease in EBF per month (P<.001) [22]. Other studies also report that using mobile phones and text messaging is feasible and has promising results in smoking cessation [23,24], diabetes education [25,26], sexual health, diet [26], and physical activity [27,28].

The mobile network in Myanmar used to be solely controlled by the government and, until recently, there was low access to mobile services by the general population. Consequently, there have been no interventions in Myanmar using mobile phones to promote community health and well-being. With political reform in 2011, Myanmar is on the verge of a communications revolution. Mobile phone prices have reduced considerably and the penetration of mobile services has increased from 2% in 2011 to 49% in 2014 [29,30]. Improved mobile phone services have enabled us to plan a randomized controlled trial (RCT) using mobile phones to promote EBF practices. This planned trial is called M528 where M stands for the mobile phone and 528 is a special number in Myanmar that refers to selfless love and other emotions and represents the bonding between mother and baby.

The objective of this study is to implement a mobile phone–based EBF promotion in pregnant women attending the antenatal clinic at Central Women's Hospital, Yangon, and to evaluate its impact on breastfeeding practices. The primary hypothesis is to test whether breastfeeding promotional text messages can help increase EBF practices in the intervention group. We hypothesize that EBF rates in the intervention group during the 6 months after delivery will be double (30%) that of the control group (15%). Although the Myanmar Multiple Indicator Cluster Survey 2010 reported that 24% of infants younger than 6 months were exclusively breastfed, only 15% of infants were exclusively breastfed until they were 6 months old [4]. We, therefore, set the control group's EBF rate at 15% and expect that the intervention group will have EBF rate at 30% at the end of the study. This is realistic as other intervention studies using text messages to promote EBF practices have reported a more than 2-fold increase in the odds of EBF. For example, a trial in China found a higher EBF rate at 6 months postdelivery in the intervention group (adjusted odd ratios [AOR] 2.58, 95% CI 1.4-3.7) [31] and a trial in Nigeria showed

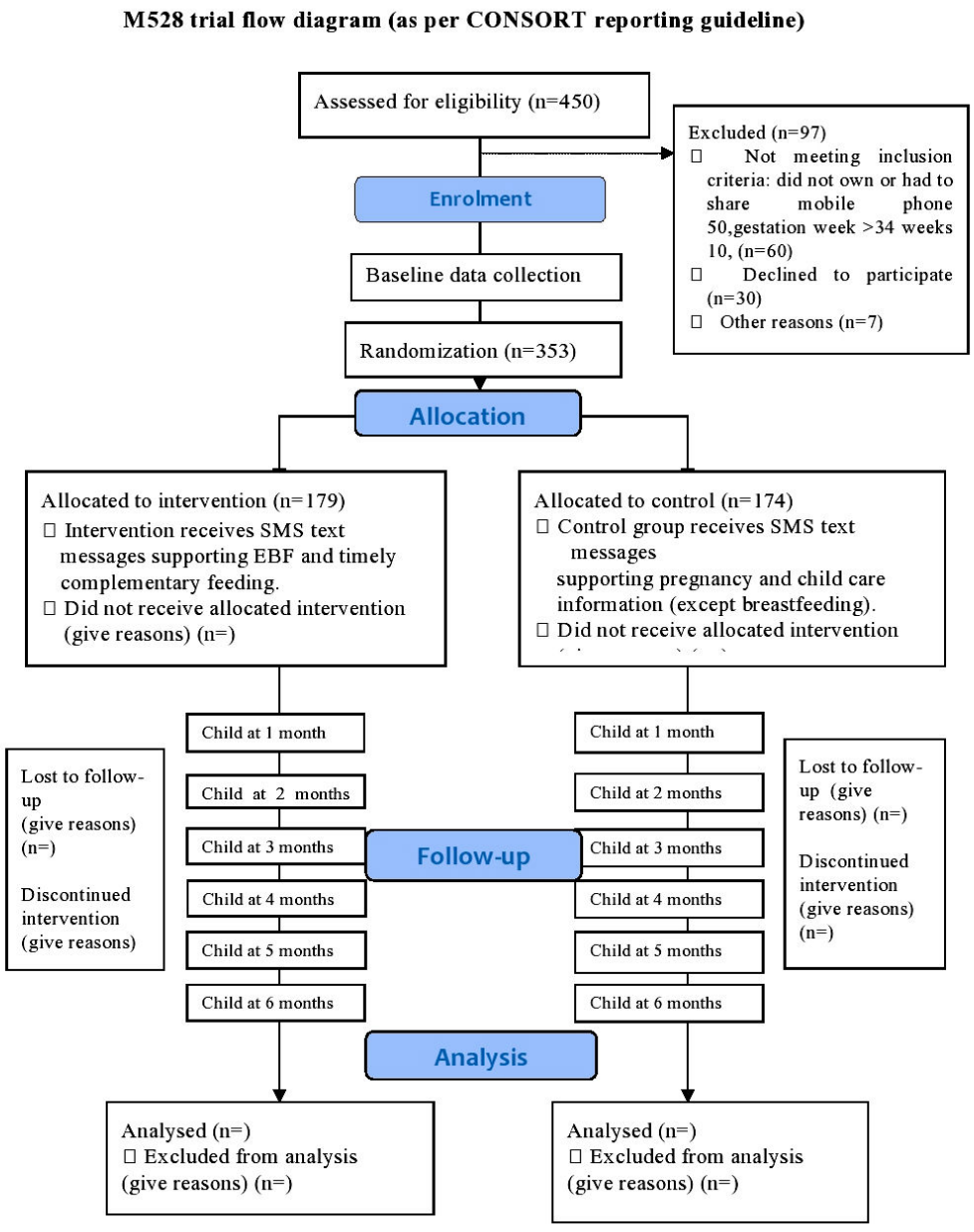
a similar result (AOR 2.40, 95% CI 1.4-4.0) [32]. Our secondary hypotheses are that receiving breastfeeding promotional text messages will result in higher appropriate infant feeding practices in the intervention group compared to that of the control group. We assessed women's feeding practices, breastfeeding self-efficacy scales, and delivery and child morbidity characteristics during follow-up. We also conducted a process evaluation at the end of the study. Our findings will also help to provide recommendations on how mHealth-based breastfeeding promotion programs can be further improved for use in wider populations.

Methods

Study Design

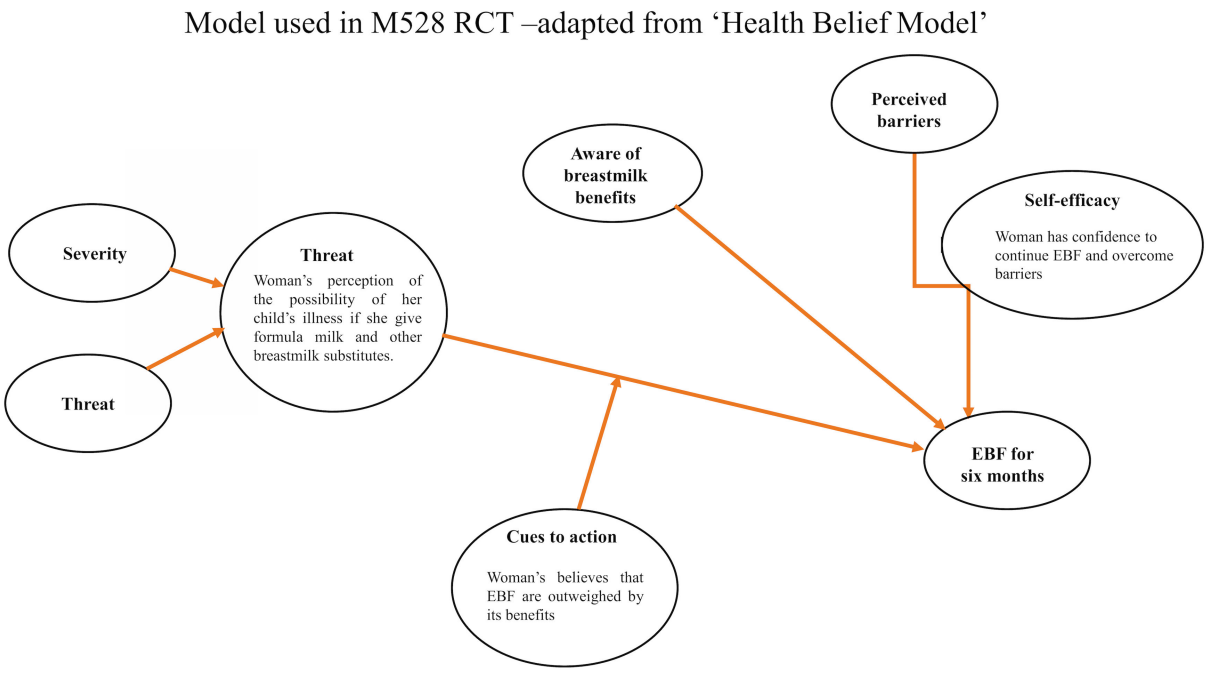
A 2-group parallel arm RCT with hospital-based recruitment and 9 months of follow-up was conducted to test the effect of a text message–based intervention for EBF promotion in participants recruited from the Central Women's Hospital, Yangon. A total of 353 women were recruited for the study. The intervention group received breastfeeding promotional messages and the control group received pregnancy- and childcare-related messages (except breastfeeding messages) from the time of recruitment until 6 months postdelivery. The study involved conducting a formative (qualitative) study to inform the trial design and to develop text messages, recruiting pregnant women, implementing the intervention, collecting data at baseline and from 1 to 6 months postdelivery by monthly phone calls, and evaluating effectiveness at the end of the study. Figure 1 summarizes the study design of the M528 RCT using the Consolidated Standards of Reporting Trials (CONSORT) template.

Figure 1. M528 trial flow diagram (as per Consolidated Standards for Reporting Trials guideline).



We used the Health Belief Model [33] that suggests that a set of beliefs, specifically beliefs about susceptibility, severity, barriers, and benefits, leads to a particular behavior. We postulate that a woman will EBF (a particular behavior) if she believes (perceived benefits) that breastmilk has all the nutrients needed for her baby for 6 months, prevents infection, and is good for the child's physical and neurological development. She will stop giving water and formula milk while her child is under 6 months of age if she believes that these could cause diarrhea and indigestion (perceived threat: a combination of perceived severity and perceived susceptibility). She will have higher perceived self-efficacy if she receives information on how to overcome barriers (perceived barriers) such as how to manage her family's influences, solve breast problems, and express breastmilk when returning to work. The Health Belief Model adapted for our study is described in Figure 2; an illustration showing how the text messages relate to the Health Belief Model is described in Textbox 2 (after stage 1: preparatory phase).

Figure 2. Model used in M528 trial—adapted from Health Belief Model.



Ethics Approval and Consent to Participate

The study has been approved by the Myanmar Ethical Review Committee, Department of Medical Research, Ministry of Health and Sports, Myanmar (approval number 7/ethic 2014) and the Department of Health, Ministry of Health and Sports, Myanmar (medical care-2/A-24/2014-659). The Ethical Review Committee, University of Sydney, acknowledged and approved the study based on the approval of the ethics committee in Myanmar. Furthermore, the M528 study trial is registered through Australian New Zealand Clinical Trials Registry [ACTRN12615000063516].

Setting

The Central Women's Hospital, Yangon, was purposely selected as it is the largest tertiary public women's hospital in Myanmar. The antenatal care clinic operates Monday through Friday and, in 2013, the hospital reported that, on average, 2000 pregnant women visited the clinic each month. The main reason for visits is to have the opportunity to deliver at the hospital free of charge because the majority of mothers attending could not afford private hospitals or clinics. In this setting, there is a higher possibility of recruiting women from a diverse range of socioeconomic backgrounds. The hospital is accredited as a baby friendly hospital initiative and follows guidelines to provide early initiation of breastfeeding. The hospital has a policy to encourage mothers to give colostrum to babies within 1 hour after birth regardless of the type of delivery.

Study Population

Inclusion criteria were women from 28 to 34 weeks gestation who could access a mobile phone (Android or Java) that could display Myanmar language fonts, who had an uncomplicated singleton pregnancy, who were able to read and write in the Myanmar language, and who lived in an area with mobile network coverage. Exclusion criteria were pregnancy complications, a multiple pregnancy, and known medical conditions including mental illness that might hinder breastfeeding.

Recruitment, Assignment, and Allocation

Participant eligibility was assessed via a hospital attendance registry (used by hospital staff) and antenatal care records (kept by the participant) in which information such as age, weeks of gestation, address, and phone numbers were recorded. At recruitment, researchers identified potential participants with the help of hospital nurses, explained the study, provided an information statement and consent form written in Burmese, and confirmed eligibility. If a woman agreed to participate, informed consent was obtained, and she was requested to

complete the baseline survey questions. The participant's mobile phone was checked for compatibility with text messages and, if needed, brief training on how to read and send text messages was provided. The recruitment process took 6 weeks (January to February 2015). Out of a total of 450 potentially eligible pregnant women, 353 were confirmed to be eligible and consented to participate in the trial. Each woman received 500 Myanmar kyats (US $0.50) to compensate for sending a text message to inform the research team of her delivery date.

Eligible women were randomized to the intervention or control group according to an allocation sequence generated by a computer program [34] with a block size of 16 to ensure a balanced group size. Each study and group number was kept in an opaque envelope to conceal the allocation sequence and securely stored. At recruitment, research team members sequentially took an envelope for each consenting participant and conducted the baseline interview. After the participant's information was recorded, the envelope was opened and the group allocation was recorded.

Blinding

Because the intervention could not be blinded, we minimized bias by ensuring both groups received messages and by not explaining in the consent and information sheets how the text messages differed between groups. The information statement provided only general information that each participant could be allocated randomly into a group; would receive messages containing information on pregnancy, childcare, and breastfeeding practices; and that the frequency of messages could vary from 1 to 3 times per week. Research staff and interviewers (via telephone) were blinded to each participant's group status although they might guess the group based on participants' responses. To minimize bias, we also blinded research staff to the trial aims and hypotheses.

Sample Size Determination

Stata version 13.0 (StataCorp LLC) was used for sample size estimation and data analysis. Sample size was calculated with the assumptions of 80% power, 5% 2-sided alpha, and 13% expected loss at follow-up. The EBF rate of Myanmar children at 6 months of age was 15% [4], and we hypothesize that EBF in the intervention group will be increased 2-fold. The estimated sample size was 312 (156 per group) and the final sample size requirement was 353 participants to allow for 13% loss at follow-up.

Data Collection

Baseline data were collected from participants during recruitment. Follow-up (outcome) data were collected by monthly phone calls at 1 to 6 months postdelivery. Process evaluation (evaluation survey and in-depth interviews) was undertaken at completion of the study. Quantitative data were collected on Android tablets using the Dimagi CommCare app [35] to reduce errors and facilitate data processing. All questionnaires were pretested prior to transferring to tablets. Full details of the baseline, follow-up, and process evaluation measurements and timing of each measurement are shown in Table 1.

Baseline Data Collection

Baseline questionnaires comprised instruments which have been validated and tested for reliability and were adapted from the 2011 Myanmar Multiple Indicator Cluster Survey [4] 2015, Myanmar census questionnaires [36], the 2011 Demographic and Health Survey, Bangladesh [7], and a 2012 study from Shanghai, China [37]. At baseline, participants were asked to provide information on their socioeconomic status, previous pregnancies and breastfeeding history, knowledge and sources of breastfeeding information, confidence to breastfeed and perceived self-efficacy to breastfeed, intention to breastfeed, and intended breastfeeding patterns.

Table 1. Summary of instruments used at various times in the M528 trial.

Instruments	Baseline	Postpartum month					
		1	2	3	4	5	6
Individual socioeconomic factors (participant and husband): age, sex, ethnicity, religion, education, occupation	x						
Household factors: income level, wealth index	x						
Previous pregnancy, childbirth and breastfeeding experience	x						
Breastfeeding knowledge level (high/medium/low)	x						
Intention and confidence to exclusively breastfeed	x						
Breastfeeding self-efficacy scores (high/low)	x	x		x		x	
Postdelivery survey: date of birth; place of birth; type of delivery; and child's birth, weight, and sex		x					
Child morbidity characteristics: signs and symptoms of fever, cough, respiratory tract infection, diarrhea, dysentery		x		x		x	
Breastfeeding and other feeding follow-up module—24-hour recall and 1-month recall		x	x	x	x	x	x
Social desirability scale (high/medium/low)						x	
Process evaluation on mHealth (intervention group only): frequency of text messages received, user-friendliness of the messages received, perceived relevance of messages, trust in messages, understanding of messages, and new information learned or not							x

We will examine the relationship between breastfeeding duration and self-efficacy using self-report Likert scales (no confidence= 1, somewhat confident= 2, sometimes confident= 3, confident= 4, very confident= 5) [38,39]. With 5 levels of responses to 33 items, total scores range from 33 to 165 and will be categorized as low self-efficacy (1 to 82) and high self-efficacy (83 to 165).

Follow-Up Data Collection

Follow-up comprised a postdelivery survey, feeding follow-up assessments, morbidity, breastfeeding self-efficacy, and social desirability assessments. Questionnaires have been adopted from the Global Strategy for Infant and Young Child Feeding [6] indicators for assessing infant and young child feeding recommendations by WHO [38-40], breastfeeding efficacy scales [41,42], a short version of the Marlowe-Crowne Social Desirability Scale [43], and unpublished questionnaires being used in ongoing projects in Bangladesh (MJD and ML) and Indonesia (MJD).

The postdelivery form was completed when the child was 10 days old and was used to assess his or her postdelivery status, including the date, place, and type of delivery and the child's birth weight, sex, and perinatal outcomes. The feeding follow-up form was completed every month and asked if the child was breastfed and if other liquids or foods were given in the last 24 hours and over the preceding month since the last contact (or birth for the first follow-up). Each participant completed 6 assessments of their feeding practices, including detailed information about the different types of liquids and foods (Textbox 1).

Child morbidity status and self-efficacy were assessed when the child was 1, 3, and 5 months of age using items from a validated instrument [7,41,42]. Child morbidity questions were used to record whether the child has had any signs or symptoms such as fever, cough, cold, running nose, rapid breathing, difficulty in breathing, chest indrawing, and diarrhea and dysentery. If one of these was present, we further explored the duration of illness. Breastfeeding self-efficacy was collected at 1, 3, and 5 months postdelivery to ascertain the mothers' confidence to breastfeed, the relationship between self-efficacy and breastfeeding duration, and whether text messages improved breastfeeding self-efficacy. Studies report that women with a higher perceived self-efficacy for breastfeeding tend to initiate breastfeeding and persist even through challenges, and we hope that women in our study will increase their confidence or self-efficacy to continue EBF because of the knowledge gained from the text messages they received [41,42,44,45].

Textbox 1. List of different types of liquids and foods.

Liquids or fluids:

- Plain water
- Juice or juice drinks, honey
- Oralit or any oral replacement therapy (ORS), including fruity ORS made in China
- Vitamin drops or other medicines as drops including traditional Burmese medicine
- Infant formula milk such as Nestle, Dumex, Chinese brands[a], and Red Cow
- Milk that is tinned or powdered (PEP, Red Cow) or fresh animal milk such as cow or goat milk
- Clear broth or other soup, such as chicken, beef, or fish broth
- Any other water-based liquids such as sugar water, rice water, green tea, tea, coffee mix, or soda
- Soya milk or yogurt

Semisolid and solid foods:

- Branded baby food, such as SUN, Nestle, Dumex, Chinese brands[a])
- Rice powder, cooked or blended rice, bread, noodles, porridge, or other foods made from grains such as sago
- Pumpkin, carrots, squash, or sweet potatoes that are yellow or orange inside
- White potatoes, yams, manioc, cassava, or any other foods made from roots
- Any dark green leafy vegetables such as water cress, drum stick, lady finger, and spinach
- Fruit rich in vitamin A such as ripe mango, papaya, jack fruit, oranges, and persimmons
- Any other fruits or vegetables such as banana, guava, apples, green beans, and peas
- Liver, kidney, heart, or other organ meats
- Any meat such as beef, pork, lamb, goat, chicken, or duck
- Eggs
- Fresh or dried fish, dried shrimp, or other seafood

[a]Chinese brand milk products means imported milk products from the Myanmar-China border with or without registration.

We also assessed social desirability status, which is the tendency respondents have to answer questions in a way that is viewed favorably by others (such as research team members). This can interfere with the interpretation of average tendencies as well as individual differences [43]. By measuring social desirability status, we were able to assess whether follow-up data were influenced by bias. We used the validated and reliable short version of the Marlowe-Crowne Social Desirability Scale, which is based on a subset of 13 items adapted from Reynolds and Gerbasi [43].

Intervention Procedures

Before the start of the trial, research team members received training by the principal investigator on how to collect data by tablet, conduct recruitment, implement group allocation, conduct follow-up phone calls, and monitor times to call participants. The schedule of enrollment, interventions, and assessments is shown in Table 2.

Table 2. Protocol schedule of enrollment, intervention, and assessments for M528 (average length of study duration is 36-38 weeks).

	Women at 28-34 weeks gestation	1 day after enrollment	At 36 weeks	Delivery	Age of child in months					
Enrollment					1	2	3	4	5	6
Eligibility assessment, consent, assignment, and allocation	x									
Interventions										
Both groups receive texts		x	x	x	x	x	x	x	x	x
Assessments										
Baseline survey	x									
Delivery check by text and phone calls			x	x						
Follow-up phone calls to assess										
Postdelivery status					x					
Feeding follow-up status					x	x	x	x	x	x
Child morbidity and self-efficacy scale					x		x		x	
Social desirability scale										x
Evaluation on mHealth (intervention group): phone-based survey and qualitative study										x

Intervention Group

Implementation was organized in 2 phases, preparation and intervention service delivery.

Stage 1: Preparation Phase

In developing text messages, we reviewed infant feeding literature including United Nations Children's Fund (UNICEF) and WHO breastfeeding guidelines [6,46]; Australian Ministry of Health breast and infant feeding guidelines [47,48]; Uganda breastfeeding counseling messages [49]; information and communication materials focused on infant feeding educational messages from the Department of Health [50] and Save the Children, Myanmar [51]; a similar study conducted in China [31,37], and findings from our formative qualitative study [16]. This phase was conducted in 2014 to inform the study design and involved in-depth and key informant interviews and focus group discussions with pregnant women and accompanying family members; nurses and doctors from the Central Women's Hospital; senior managers from the National Nutrition Centre, Department of Health, UNICEF, and international and national nongovernment organizations; and a private mobile company [16]. This provided valuable information for modifying the study instruments—for example, by making the module on service delivery more realistic. One key finding was a need to train mothers, particularly working mothers, on how to manually express breastmilk. We, therefore, adopted the Marmet technique [52] in messages sent at 6 to 12 weeks postdelivery.

Textbox 2. Health Belief Models and example text messages.

Benefits to child (perceived benefits):

- Breastmilk contains water and nutrients needed for your baby and is sufficient for the first six months of life.
- Breastmilk is best for your child's memory, brain development, and physical growth.
- Breastmilk is readily available, convenient, clean, safe, free, and does not need any preparation.
- Breastmilk will prevent your child from having diarrhea or pneumonia and help them recover quickly if ill.
- People who were breastfed as babies are less likely to be overweight or obese or have type 2 diabetes than those who were not breastfed.
- Colostrum (Noh-Oo-Ye), the first yellowish milk, is clean and not dirty. It contains antibodies and prevents your child from getting sick. Do not throw it away.
- Colostrum (Noh-Oo-Ye) will protect your baby from allergies, infection, and yellow skin and eyes (A-Thar-Wah).

Benefits to mothers (perceived benefits):

- If you breastfeed, your chances of having breast and ovarian cancer later in life will be reduced.
- Breastfeeding may have a natural contraceptive effect.
- Breastfeeding will help you reduce your weight after delivery and return to your original shape

Perceived barriers—grandmother's (child's grandmother) influences in adding water, honey and formula milk:

- Please share this message with your grandmother: Breastmilk alone has everything your baby needs. It has all the nutrients and water required.
- Please share this message with your grandmother: Don't use a bottle or teat. Your baby can drink up from a cup—even newborns. Cups should be wide mounted.
- Don't give in to peer pressure (from grandmothers and others) when they tell you to use formula milk after delivery.

Skilled training approach to overcome the perceived barriers for inadequate milk flow and breast problems:

- It is important to bring your baby to your breast instead of leaning over to your baby. A good latch and position is important for good milk flow.
- Make sure you have correct posture and your baby is attached properly. If your baby can suck well, you will have better milk flow and prevent sore and cracked nipples.
- If you have sore or cracked nipples, breast engorgement, or mastitis, don't give up. Take your baby off your breast for a while and try again in a little while. Also try gently massaging your breast. Frequent breast feeding can reduce pain and produce more breastmilk. If pain persists, tell your midwife or health care practitioner.

Skilled training approach to overcome the perceived barriers (especially for women who have to return to work):

- Plan to breastfeed before you return to work. Arrange with your employers/supervisors (if possible). If you go back to work, your grandmother or another carer may be able to bring your baby to work for breastfeeding.
- Expressing milk by hand is using your hand to rhythmically compress your breast so that milk comes out. You need to compress the area under the areola (the pink or brown part of the breast) behind the nipple, not the nipple itself.
- Please keep breastfeeding. Express breastmilk before you go to work. The best time is before and after work and at night time.
- Expressed milk can be safely stored in the refrigerator for 72 hours and at room temperature for 24 hours. Make sure you put breastmilk in a clean, sealed container.

Perceived threat (perceived susceptibility and severity):

- Do not give water, honey, sweet fluids, or anything else (such as rice powder or porridge) to your baby. These could make your child sick and slow your milk flow.
- Formula milk may cause your baby to become constipated because it is harder to digest than breastmilk.
- Formula milk may cause diarrhea if prepared in an unhygienic way.
- Your breastmilk has all the essential things needed for your baby's brain and eye growth, whereas formula milk does not.
- Don't start giving any semisolid or solid food to your baby before he or she is 6 months old. Your baby's stomach is too small to digest food yet. It can also cause diarrhea.

Self-efficacy (coping efficacy to overcome barriers and to continue EBF):

- Breastmilk has all nutrients in perfect balance for your baby and is an ideal food for newborns and infants. Do not be pressured by your husband, parents, or in-laws to stop breastfeeding.
- Don't stop breastfeeding. You can overcome barriers!

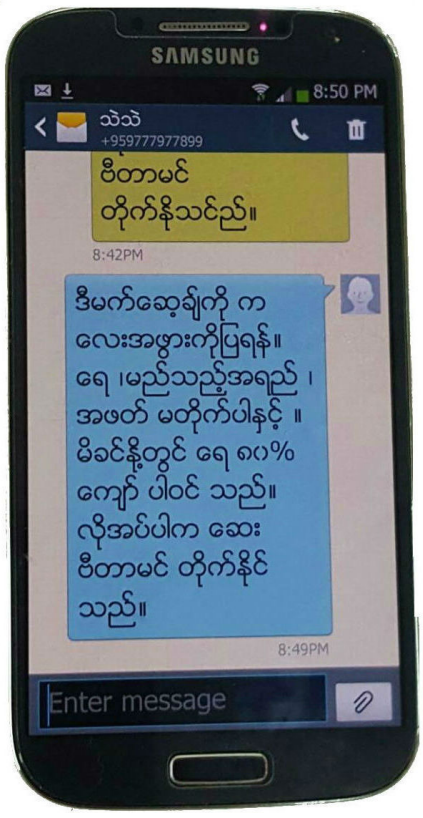
- Congratulations! You have successfully breastfed your child for 6 months. Please continue. Your child will thank you. (Note: Improved self-efficacy is linked with training mothers to EBF.)

We also saw the need to revise the inclusion criteria to include only women past 28 weeks' gestation because the majority of women who visited the antenatal clinic did so only after they were past this point in their pregnancy. We also revised the required educational status to ability to read and write instead of primary school passed. We sought advice from Dr Nina Berry, a certified breastfeeding counselor from the University of Sydney who has had experience working in Myanmar, and antenatal clinic nurses from the study hospital. Developed messages were pretested with 15 pregnant women meeting the inclusion criteria and were revised before finalization. Messages were customized to pregnancy gestation and children's age and categorized into 2 key periods: 28 weeks of pregnancy to delivery and delivery to the child at 6 months of age. We created messages that were simple, locally acceptable, and culturally appropriate. The developed messages were relevant to early child development milestones and the specific needs of expectant and new mothers in relation to EBF. The focus of the messages in relation to the Health Belief Model (described in the study design section) [33] is summarized in Textbox 2. We set up "delivery check messages" sent out automatically when participants reached 36 weeks' gestation. An example message sent was "Have you delivered? If yes, please reply 1, if no, please reply 2." If the server received a reply of 1, then messages were immediately changed from prenatal to postnatal. If there was no response after 38 weeks' gestation, we followed up with a phone call or checked hospital registrations to ascertain if the participant had delivered.

Stage 2: Intervention Service Delivery

The intervention was delivered over 9 months—from recruitment to 6 months postdelivery. Text messages were sent to the intervention group 3 times per week (Tuesday, Thursday, and Saturday) in the evening using CommConnect [35], Telerivet [53], and a local company that has an official contract with mobile operators and experience sending bulk SMS messages. Each text message has approximately 160 characters written in Myanmar fonts (Zawgyi font; Myanmar font systems are not yet standardized but we selected the Zawgyi font because it is the most commonly used font in Myanmar). If a participant withdrew or experienced the death of their child, we stopped messaging. The numbers of messages received were the total number of weeks in the study × the number of messages sent per week. The total number of weeks was 38, assuming that the participant was recruited at 28 weeks' gestation, delivered at 40 weeks (term pregnancy), and remained in the study until the child reached 6 months. Therefore, the intervention group received up to 114 text messages. All participants received the usual hospital antenatal, intra- and postpartum care, and infant feeding support regardless of their assigned group. See Figure 3 for example text message.

Figure 3. Example of breastfeeding promotion text message.



Control Group

In designing the control group, we followed the recommendations made in a review article on the design of control groups [54]. To minimize intervention bias, we sent nonbreastfeeding-related text messages with mainly pregnancy- and childcare-related content but at a lower frequency (once per week). Messages were developed after reviewing the literature about pregnancy and childcare education, including WHO online resources [55,56] and information and communication materials about infant feeding produced by the Department of Health [50] and Save the Children, Myanmar [51]. Messages included the importance of following recommended pregnancy care such as taking iron and folic acid regularly, following a balanced diet, getting regular exercise, making regular health center visits, and identifying danger signs before delivery. Examples of message topics after delivery include following recommended baby immunization schedules, how to practice proper infant care, and how to protect the baby from mosquitoes to avoid malaria. Each control participant received an estimated 38 messages (1 per week) over 9 months, which were informed by findings from the formative study [16].

Outcome Measures

The primary outcome is the rate of EBF at 1 to 6 months of the infants' age measured at monthly intervals after delivery. Secondary outcomes are median duration of EBF and rates of early initiation of breastfeeding (within 1 hour after birth); predominant breastfeeding; current breastfeeding; bottle feeding; and early introduction of solid, semisolid, or soft foods at 1 to 6 months of infant's age (measured at monthly intervals) [38-40]. We used WHO infant and young child feeding definitions for this study, and definitions of these outcomes are described in Multimedia Appendix 1 [38].

Process Evaluation

An evaluation of the use of mobile phones to promote breastfeeding practices was conducted with participants from the intervention group. Information on text delivery success, user experiences (user-friendliness), acceptability (trust), comprehension, new information learned, and feedback from received messages was assessed by trained callers during phone calls at 5 to 6 months after delivery. We measured acceptability (proportion of participants who trust the messages), comprehension (proportion of participants who can describe the last message received), and new information learned (proportion of participants who indicate they learned new information about breastfeeding). These instruments have been widely used in mHealth evaluations in other countries [20,57-60] and took about 10 minutes to administer.

At completion, a qualitative study was conducted with intervention group participants. Based on information from follow-up calls, participants were split into 3 subgroups: EBF for 6 months, predominant and other types of breastfeeding (excluding EBF), and breastfed for less than 1 month only. In-depth interviews were held with approximately 25 women (7 to 9 women from each group) using semistructured guidelines. We explored user experiences in receiving SMS text messages, perceptions about the number of messages received, message delivery success, acceptance of the service delivery model, and effect of messages on breastfeeding practices. We expected that this number of participants would allow us to reach saturation point [60]. There were variations in the numbers of participants we could interview based on breastfeeding outcome, participant's availability, logistic reasons, and feasibility of the study.

Data Analysis

Quantitative data were collected via tablets and automatically submitted to the Dimagi server from which we could monitor data and generate reports. Stata software version 13 (StataCorp LLC) was used for data analyses. The intervention and control group outcomes will be compared using intention-to-treat principles [61]. Descriptive analyses were used to summarize participant baseline characteristics and breastfeeding practices. Likert scales were analyzed using Mann-Whitney U tests or cumulative odds ratios and proportions between groups using chi-square tests. Duration of EBF was compared by survival analyses with log-rank tests for between-group comparisons. If differences in baseline characteristics of the groups are identified, multivariable analyses will be undertaken. We report results using the CONSORT guidelines for reporting of randomized trials [62]. As follow-up data collection had to rely on the mothers' self-reporting alone, we adjusted the potential social desirability bias [43] in our analyses to confirm the accuracy of self-reported outcome measures.

For process evaluation, we used Stata software for survey data analysis. We conducted descriptive analyses to summarize participant baseline characteristics and their experiences and feedback about receiving text messages. Text message delivery success was measured by the frequencies of messages received, and proportions were compared with chi-square tests. For the qualitative study, we used thematic analysis. All digitally recorded interviews were transcribed verbatim in Burmese in Microsoft Word and were reviewed to check for accuracy and translated to English. A list of thematic codes was developed by MPH, which was independently reviewed and verified by AA. The data were then be manually coded by MPH for emerging themes, which were again verified by other investigators and the most relevant themes are summarized in a document.

Results

The targeted 353 pregnant women were recruited between January and March 2015. Baseline data have been collected. SMS messages have been developed, pretested, and sent to the women from both groups. Follow-up data collection via phone calls is now complete. Data analysis is still ongoing and results are to be expected soon. This is the first RCT study examining the effects of mobile text messages in promoting EBF.

Discussion

Implications of the Research

We hope to achieve our outcomes as SMS text messaging is increasingly being applied to improve reproductive, maternal, neonatal, and child health with growing evidence of its

effectiveness [20-28,31,32,59,60]. This study is important as our intervention will leverage the power of mobile phone technology at an appropriate time following the opening up of the telecommunications market in Myanmar. Incorporating feedback from the community and mobile service providers prior to the study was a key element in the study design. We could envisage similar larger scale interventions implemented within the health system with women recruited from other public and private hospitals or community settings in the future. We also acknowledge that a number of factors may interfere with the success of the intervention. We anticipate the possibility of mobile coverage variation across geographic areas as the launch of mobile operators only started in 2014. Another barrier is that people often change phone numbers in order to receive better network and promotional prices leading to difficulties in sending text messages and making follow-up phone calls. Successfully upscaling the intervention would have the potential to improve child nutrition and consequently to reduce neonatal and infant morbidity and mortality where causes are associated with suboptimal breastfeeding practices. With the endorsement of Sustainable Development Goals, nutrition is central to 12 of the 17 development goals [63] and the role of breastfeeding is essential in achieving these goals. We also anticipate that continued growth in the coverage of the mobile network could attract the Ministry of Health and Sports and policy makers to implement mHealth-based behavior change interventions in national programs.

Strengths and Limitations

A key strength of our study is the use of an RCT design to assess the impact of text messages on improving breastfeeding practices. Although the trial cannot be fully blinded, research team members who recruit participants and conduct follow-up phone calls are blinded to group allocation. By sending messages with different content to both control and intervention groups, we reduce the possibility of indirect effects of participants receiving health messages on the targeted behaviors. Both groups receive pregnancy and child healthcare-related text messages, but only the intervention group receives messages about breastfeeding. The intervention is feasible to implement because of the significantly reduced prices of subscriber identity module (SIM) cards, increased availability of cheap smart phones, and improved coverage of a 3G network. In addition, female literacy is high with 94% of urban women and 84% of rural women able to read text messages [36]. The timing of the study may allow new investments for mHealth-based EBF promotion interventions.

Limitations include recruitment from only 1 hospital, which will reduce the generalizability of results. To date, only major cities in Myanmar have reliable access to the mobile network but this is changing rapidly as the network is expanded, offering opportunities to adapt the intervention for rural populations. The hospital selected for recruitment, which has a patient population of women from diverse ethnic and socioeconomic backgrounds, is the largest public hospital providing free quality delivery care service. Women come from all over the country, including from rural and urban slum areas. It is likely that the participants have similar feeding practices to women from other areas as feeding practices only differ slightly between states and regions [4]. We acknowledge that the intervention group has more frequent SMS text messages than the control group and it could be a limitation of the study. However, we assume that the difference in SMS text message frequency might not constitute an intervention. Several studies including studies conducted in Australia [22], Iran [64], and Korea [65] delivered text messaging service once a week to the intervention groups and findings reported that these interventions were effective.

Another limitation is that there may be technological challenges when participants are not familiar with the use of mobile phones. However, we have compensated for this by providing training. As with other mobile phone programs, we anticipate a possible low response rate because participants may not answer calls, may switch off their phone, or may change their phone number. Solutions to these problems include recording alternate contact numbers during recruitment, calling repeatedly if the phone is powered off, or trying to reach the participant based on the suggested time to call.

Conclusions

This is the first Myanmar RCT to test the effectiveness of mobile text messaging (mHealth) in promoting EBF practices. Our results will help determine whether text messaging is an effective and feasible method for promoting appropriate feeding practices and will inform further research to assess how this model could be replicated in the broader community.

Acknowledgments

MPH is supported by an Australian Leadership Award of the Government of Australia for her PhD studies. The Sydney Medical School Foundation and Post Graduate Research Support Scheme, Sydney Medical School, University of Sydney, both provided grants for the development of the intervention and conduct of the trial.

The authors wish to acknowledge respondents (pregnant women, family members, and institutional staff from the Department of Health in the Ministry of Health and Sports, Myanmar, the private mobile company, and the international and national nongovernmental organizations) who participated in the formative study and women who participated in the intervention for their valuable time. We also acknowledge the support from the Ministry of Health and Sports, Myanmar, and authorities from the Central Women's Hospital, Yangon, and Ethical Review Committee, Department of Medical Research, Ministry of Health and Sports, Myanmar, for approving the study and ethical clearance. Special thanks to Dr Thein Thein Htay, Deputy Minister (retired), Ministry of Health and Sports, Myanmar, for supporting the approval of the study. We also acknowledge Dr Nina Berry, a breastfeeding promotion expert, University of Sydney, Australia, for providing input into the development of breastfeeding promotional text messages. We would like to thank Dimagi for allowing the use of their pro-bono scheme for data collection.

We would also like to thank Saijai Liangpunsakul from Dimagi and Jessica Hall from The University of Sydney for technical support in developing the CommCare applications.

Authors' Contributions

Overall MPH conceived the study design, led the development and conduct of the trial. All authors (MPH, ML, and MD) contributed to the design of the trial and development of the behavior change SMS message contents. MPH developed and translated SMS contents and questionnaires into Burmese. MJD informed the sample size calculation, analysis methods, and the method for allocation of treatments. MPH coordinated and conducted the study, including preparing ethics applications, recruiting participants, conducting baseline study, building questionnaires in CommCare, supervising SMS sending and follow-ups, conducting the evaluation, and drafting the manuscript. AA contributed in the qualitative analysis section. All authors edited, read, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Presentation of the study at World Conference in Public Health, Melbourne.

[PPTX File, 2MB - resprot_v6i6e126_app1.pptx]

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Abbreviations

AOR: adjusted odds ratio
CONSORT: Consolidated Standards of Reporting Trials
EBF: exclusive breastfeeding
RCT: randomized controlled trial
SIM: subscriber identity module
SMS: short message service
UNICEF: United Nations Children's Fund
WHO: World Health Organization

Edited by G Eysenbach; submitted 10.03.17; peer-reviewed by M Hassandra, H Jiang, R Biviji; comments to author 19.04.17; revised version received 01.06.17; accepted 02.06.17; published 28.06.17.

Please cite as:
Hmone MP, Li M, Alam A, Dibley MJ
Mobile Phone Short Messages to Improve Exclusive Breastfeeding and Reduce Adverse Infant Feeding Practices: Protocol for a Randomized Controlled Trial in Yangon, Myanmar
JMIR Res Protoc 2017;6(6):e126
URL: http://www.researchprotocols.org/2017/6/e126/
doi:10.2196/resprot.7679
PMID:28659252

Protocol

The Effect of Core Stabilization Exercise on the Kinematics and Joint Coordination of the Lumbar Spine and Hip During Sit-to-Stand and Stand-to-Sit in Patients With Chronic Nonspecific Low Back Pain (COSCIOUS): Study Protocol for a Randomized Double-Blind Controlled Trial

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Abstract

Background: Chronic nonspecific low back pain (CNLBP) is among the most prevalent health problems. Lumbar spine and hips kinematics and coordination can be affected in CNLBP. The effects of exercises on the kinematics and coordination of lumbar spine and hips during sit-to-stand (STS) and its reverse have not been evaluated.

Objective: The aim of this study is to investigate the effect of core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in CNLBP patients.

Methods: COSCIOUS is a parallel randomized double-blind controlled trial. A total of 30 CNLBP patients and 15 asymptomatic participants will be included. The kinematics and joint coordination of the lumbar spine and hips will be evaluated during STS and its reverse using a motion capture system. The participants will be asked to sit in their usual posture on a stool. Reflective markers will be placed over the T12, S2, anterior and posterior superior iliac spines, greater trochanters, and lateral femoral epicondyles of both legs. The participants will be instructed to stand up at natural speed, remain in the erect posture for 3 seconds, and then sit down. Kinematic variables of the lumbar spine and hip will be computed. Afterward, the CNLBP participants will be allocated at random to receive one of 2 interventions: core stabilization or general exercise. Treatment sessions will be held 3 times per week for 16 sessions. After intervention, CNLBP participants will be assessed again.

Results: Funding for the study was provided in 2016 by Iran University of Medical Sciences. The study is expected to last approximately 12 months, depending on recruitment. Findings on the study's primary outcomes are expected to be finalized by December 2017. The results of the study will be published in a peer-reviewed journal.

Conclusions: This investigation will evaluate the effects of core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with CNLBP. In addition, the effects of CNLBP on STS and its reverse will be investigated in COSCIOUS.

Trial Registration: Iranian Registry of Clinical Trials IRCT2016080812953N2; http://en.search.irct.ir/view/32003?format=xml (Archived by WebCite at http://www.webcitation.org/6qjTWd4Az)

(JMIR Res Protoc 2017;6(6):e109) doi:10.2196/resprot.7378

KEYWORDS

kinematics; lumbar spine; hip; chronic nonspecific low back pain; joint coordination; core stabilization exercise

Introduction

Low back pain (LBP) is defined as pain between the 12th rib and inferior buttock crease with or without leg pain [1,2]. According to the Global Burden of Disease Study, LBP is a major cause of years lived with disability in all continents and economies [3], and it is one of the main causes of absenteeism in industrialized societies [4]. Chronic low back pain (CLBP) is generally defined by symptoms that persist for a period of longer than 3 months (12 weeks) [5,6]. However, there is no precise definition of CLBP in the literature [7]. In some studies, CLBP is described as pain that lasts longer than 7 to 12 weeks, whereas the others define this condition as pain that lasts longer than expected with conventional treatment [7]. Due to no consensus regarding the definition of CLBP, there is a wide variation in the prevalence estimates reported in the literature [8]. However, Parthan et al [8] mentioned that the prevalence of CLBP ranges from 4% to 14%.

LBP is frequently associated with changes in the mobility of the lumbosacral region and hip [9-12]. Normal spinal mobility is required for optimal activities of daily living performance, and it has been shown that impairment of spinal mobility can result in various forms of functional disabilities [13], which may have serious adverse effects on quality of life [12]. Patients with LBP have been shown to have some limitations in both spinal and hip motion that compromise their function. In addition, Marras and Wongsam [14] indicated that the coordination between the lumbosacral region and hip is decreased during standing forward bending in patients with LBP. However, their simple descriptions of range of motion (ROM) and a simple forward bending task that do not adequately explore coordination between movements of the lumbosacral region and hips limit the generalizability of their findings to the functional tasks [12-14].

Sit-to-stand (STS) movement and its reverse, which are considered fundamental prerequisites for daily activities, are repeated many times throughout the day [12]. It has been shown that this movement could be performed about 60 times per day in workers [15]. In addition, STS movement is a skill [16], and the ability to perform this movement is a key factor in the maintenance of functional independence [17]. The manner in which STS movement is described depends somewhat on the aim of the study. For example, in the Roebroeck et al [18] study, STS movement is defined as traveling the body's center of mass (COM) upward from a sitting position to a standing position without losing balance [18]. Vander Linden et al [19] defined STS movement as a transitional movement to the upright posture and requiring movement of the COM from a stable position to a less stable position over extended lower extremities. Schenkman et al [20] defined STS movement in more detail and divided it into 4 phases. Phase I (or *flexion-momentum phase*) begins with initiation of the movement and terminates just before the buttocks are lifted from the seat of the chair (lift-off). During this phase, the trunk and pelvis rotate anteriorly and the femurs, tibias, and feet remain stationary [20]. Phase II (or *momentum-transfer phase*) starts when the buttocks are lifted and terminates when maximal ankle dorsiflexion is achieved. During this phase, the COM moves anteriorly and upward [20]. Phase III (or *extension phase*) is begun just after maximum ankle dorsiflexion and completes when the hips first cease to extend, including leg and trunk extension. This phase is terminated when the hip extension angular velocity reaches 0° per second [20]. Phase IV (or *stabilization phase*) initiates after hip extension angular velocity reaches 0° per second and terminates when all motion associated with stabilization is completed [20]. Furthermore, Shum et al [12] divided STS movement into 2 phases: flexion and extension. The flexion phase begins with initiation of the movement and terminates when maximum flexion of the lumbar spine and hips is achieved (first 2 phases of Schenkman et al [20] classification). The extension phase starts just after phase I and continues until the end of the movement (last 2 phases of Schenkman et al [20] classification).

In 2005, Shum et al [12] evaluated the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with acute LBP using an electromagnetic tracking device (3SPACE Fastrak system). The results of their study indicated that the mobility of the spine and hips and contribution of the lumbar spine relative to the hip were decreased in individuals with acute LBP. Furthermore, the lumbar spine–hip joint coordination was significantly altered in acute LBP subjects [12]. However, this study was conducted on acute LBP patients, and the data obtained from these participants is not representative of the population with chronic nonspecific low back pain (CNLBP). In addition, Shum et al [12] evaluated only the kinematics and joint coordination, and the effect of intervention on the kinematics has not been assessed. They recommended that further research is needed to evaluated the effect of intervention.

A core stabilization exercise program is described as facilitation of the deep musculature of the spine (primarily the transversus abdominis or multifidus) at low-level sustained isometric contraction, integrated into exercise and finally, progressing into functional tasks. The core stabilization exercise uses motor learning principles to facilitate coordination of the deep musculature of the spine [21-23]. It is usually delivered in 1:1 supervised treatment sessions and sometimes comprises palpation or ultrasound imaging or the use of pressure biofeedback units to provide feedback about the activation of trunk musculature [23].

To the best of authors' knowledge, this study for the first time aims to investigate the effect of core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with CNLBP (COSCIOUS). The main objectives of COSCIOUS are as follows:

- To determine the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with CNLBP and asymptomatic participants
- To determine the effect of core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with CNLBP

Macedo et al [24] mentioned that core stabilization exercise can optimize the control and coordination of the spine. However, there is not sufficient evidence to clearly support this claim that core stabilization exercise has superior effects on joint coordination compared to general exercise. Therefore, the secondary objective of this study is to determine the effect of general exercise on the kinematics and joint coordination during STS and its reverse in CNLBP. We hypothesized that there are significant differences between the results in patients with CNLBP and healthy participants during STS and stand-to-sit movements. In other word, ROM, maximum displacement, and angular velocity of the lumbar spine and hips would be decreased in CNLBP. Furthermore, we hypothesized that exercise therapy would have a significant positive impact on the kinematics and coordination in CNLBP patients. It is hoped that COSCIOUS would help clinicians and physical therapists evaluate the functional disabilities of patients with CNLBP, who are a big population in LBP patients. In addition, we hope that if this study exercise therapy protocol has a more positive effect on the kinematics and joint coordination, it can be used as a guideline for the treatment of functional disabilities (especially this important functional movement) in populations with CNLBP.

Methods

Study Design and Ethics

COSCIOUS is a parallel, randomized, double-blind controlled trial with 2 experimental groups and one asymptomatic (control) group. It is a part of the PhD thesis of the first author (MRP) and will be conducted in the biomechanics laboratory located at the School of Rehabilitation Sciences, Iran University of Medical Sciences (Tehran, Iran). The level of evidence of this investigation is level Ib. Ethical review and approval for COSCIOUS was obtained from the Research Ethics Committee at Iran University of Medical Sciences (Ethical Approval Number: IR.IUMS.REC 1395.9211342207) on July 27, 2016. The trial is registered at the Iranian Registry of Clinical Trials [IRCT2016080812953N2].

Participants

A total of 30 patients with CNLBP and 15 demographically matched asymptomatic (healthy) participants will be recruited for COSCIOUS. The sample size of CNLBP patients is determined based on previous studies that have evaluated the effect of lumbar extension exercise on the kinematics of the lumbar spine and hips during a common daily activity [25,26]. Steele et al [26] calculated the sample size for their study and reported that a minimum of 7 participants would be required in each group to achieve 80% power at an alpha level of $P \leq .05$ [26]. Therefore, 45 participants will be divided into 3 groups: 2 experimental groups (15 patients with CNLBP in each group) and one healthy control group (15 asymptomatic participants). Considering some attrition, the sample size was increased to 15 participants in each group. The CNLBP patients will be identified and recruited by posters, emails, and word of mouth from the university and the surrounding locality. Direct referral also will be provided from 2 orthopedic surgeons and 2 neurologists in Tehran. Inclusion criteria of COSCIOUS are as follows:

- CNLBP (LBP persisting for more than 3 months in the absence of an underlying pathology)
- Aged between 18 and 40 years
- Pain between 3 and 6 at rest on a 0- to 10-point pain visual analog scale (VAS), where 0 represents no pain and 10 is the worse pain imaginable
- Ability to perform STS movement and its reverse without an aid
- No contraindication for exercise
- No obvious deformity of the spine, pelvis, and lower extremities
- No autoimmune diseases (eg, rheumatoid arthritis) [12]
- No pregnancy

In this study, we will try to balance some of most important prognostic indicators of LBP such as educational status, smoking, working status, age, gender, and pain intensity in 2 treatment groups [27,28]. This strategy will help minimize the effects of confounding variables. Participants who do not complete the treatment sessions (absence for 3 consecutive or a total of 5 sessions) will be excluded from the study. Before participation in this study, procedure of this investigation will be explained both verbally and in writing, and written informed consent will be obtained from all participants. In addition, the participants will be assured that their personal information will be kept confidential (confidentiality principle). Participants will be identified only by initials and participant number on the research notes. All study results and completed questionnaires will be anonymized. All trial documents will be stored securely and not accessible to people outside of the research team. Participants will be withdrawn from this investigation if there are any concerns regarding informed consent.

Randomization

Each CNLBP participant will be randomized to a general exercise group or a core stabilization exercise group with a ratio of 1:1. Randomization will be performed using a block-balanced randomization technique with 4 character blocks containing letters A and B. After randomizing, the randomization schedule will be transferred into written instructions and will be placed in sequentially numbered, opaque, sealed envelopes. The CNLBP participant will be blinded to which intervention group they are in until the end of the study. The procedure will be performed by an investigator who will not be involved with participant assessment, allocation, or treatment. The

randomization schedule is known only to a physical therapist who treats the patients. The male physical therapist (MRP) assessing participants before and after the treatment will also be blinded to group allocation, and the patients will be asked not to disclose this to the physical therapist.

Examiners

Participants will be evaluated by a male physical therapist (MRP) who is a doctoral candidate with more than 6 years of clinical experience. In addition, CNLBP patients' treatment will be performed by a female physical therapist who is a master's degree student with more than 10 years of clinical experience in orthopedic physical therapy and certified in manual therapy.

Equipment

Pain will be measured by the use of a 100 mm point VAS, and functional disability will be measured using the Persian translated version of the Ronald-Morris Disability Questionnaire (RMDQ). The RMDQ is a self–administered disability measure that was first published in 1983 [29]. It provides a tool for measuring the level of functional disability experienced by a patient suffering from LBP. The RMDQ includes 24 statements relating to the individual's perceptions of their LBP and associated disability divided into 6 domains: physical ability and activity (15), sleep and rest (3), psychosocial (2), household management (2), eating (1), and pain frequency (1) [29]. The RMDQ is designed to take about 5 minutes to complete, without any assistance from the administrator. Validity and reliability of the Persian translated version of the RMDQ has been evaluated by Mousavi et al [30], who reported high correlation between the results of this questionnaire and the physical functioning scales of the Short Form Health Survey (r=–0.62) and excellent reliability (intraclass correlation coefficient =0.86). In addition, Mousavi et al [30] concluded that the Persian translated version of the RMDQ can measure functional status in Persian-speaking patients with LBP. The RMDQ has been selected for measuring functional disability because Parthan et al [8] stated that the RMDQ is the most responsive instrument and is recommended for clinical trials in CLBP.

STS and its reverse kinematic variables will be captured at a sample frequency of 100 Hz using good resolution (1.3 megapixel) cameras and a 3-dimensional motion capture system (Qualisys AB). Kinematic data will be analyzed using Qualisys track manager (QTM) software (Qualisys AB), MatLab version R2015b (MathWorks Inc), and Excel version 2016 (Microsoft Corp).

Motion Capture System

A 3-dimentional approach will be used for data collection. However, only kinematic data in the sagittal plane will be used for analysis. According to Shum et al [12], motions out of the sagittal plane have insignificant amplitudes and cannot be used for analysis. A total of 6 Oqus 300 cameras (Qualisys AB) will be set up and angled in a manner to decrease hidden spots that might obscure data collection. In addition, the QTM software will be used to synchronize the 6 Oqus 300 cameras that record marker motion. The cameras identify infrared reflective markers which are attached to the participants and output 3-dimensional coordinates for each marker. Prior to testing, the motion system will be calibrated by recording an L-frame and dynamic movement of a T-wand for 60 seconds. After data collection, the markers will be labeled according to the anatomical landmark to which each marker is attached.

Marker Setup

A total of 14 reflective markers will be placed on anatomical landmarks. Lumbar spine segment is modeled by placing 2 25.4 mm spherical markers on the T12 and S2 spinous processes [31]. The intercrestal [32] or intercristal line [33]—the line joining the superior aspect of the iliac crests posteriorly—will be used to find the L3 spinous process or L3-L4 spinal level [34,35]. Once the L3 spinous process or L3-L4 spinal level is identified, the physical therapist will palpate the spinous processes in the midline and trace them from inferior to superior to find the T12 spinous process. The posterior superior iliac spines (PSISs) line—the line joining the right and left PSISs—will also be used to find the S2 spinous process [34]. Furthermore, 4 14.0 mm spherical markers will be placed on the anterior superior iliac spines (ASISs) and PSISs of both sides to the define pelvis segment. In order to define femur segments, 8 14.0 mm spherical markers will be placed on the right and left greater trochanters, lateral femoral epicondyles, calcaneuses, and base of the 5th metatarsals. Markers will be placed by the same investigator (MRP) for all trials. Marker trajectories will be used to calculate the position and orientation of the anatomical frames of the 4 segments (pelvis, lumbar, and 2 hips). Sagittal lumbar angle is defined as the angle between the lumbar and pelvis segments. In addition, sagittal right hip (RH)/left hip (LH) angles are defined as the angle between the right and left femur and pelvis segments. The joint coordinate system [36] will be used to calculate sagittal joint angles.

Procedure

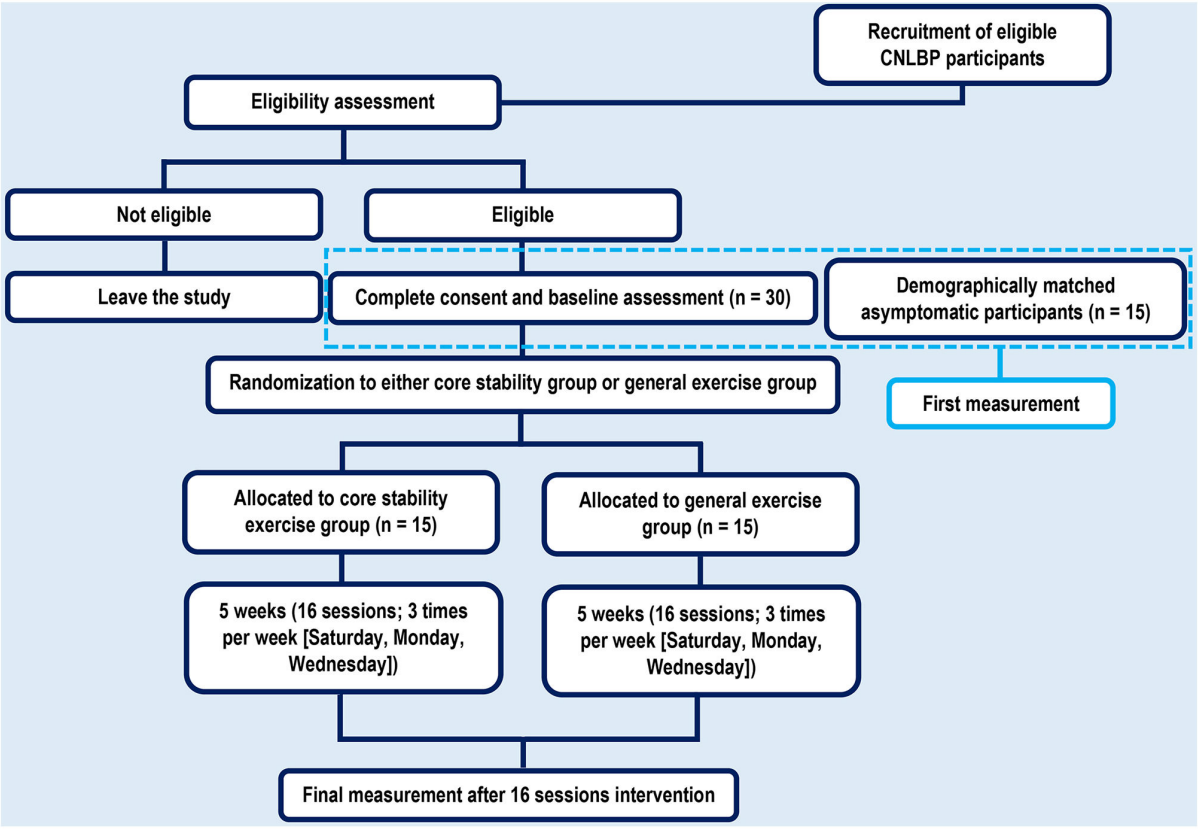
Initial Assessment

After the recruitment process is complete and agreement to participate is obtained, participants will be brought into the biomechanics laboratory of the School of Rehabilitation Sciences, Iran University of Medical Sciences (Tehran, Iran). To ensure the activity is as natural as possible, few constraints will be placed on the procedure of STS movement and its reverse. Participants will not be allowed to use their hands to push up, and the feet should stay on the floor [12]. In order to standardize head posture and prevent the negative impact of the thoracic and cervical spines on lumbar spine kinematics, a visual target (white A4 paper with a black circle drawn upon it) will be adjusted to eye level in front of participants [31]. Data collection will begin with the capture of a reference standing posture. Then, participants will be asked to sit in their usual posture on an adjustable stool with neither armrest nor backrest. The stool provides support from the ischial tuberosities to the middle of the thighs. Foot placement will not be restricted and participants will be requested to relax their arms, hanging them next to their thighs. The stool height is 110% of knee-floor length, which is defined as the distance between the floor and the apex of the fibular head [12]. Participants will be instructed to stand up at their self-selected normal speed following a loud voice command ("Start") and remain a comfortable and erect posture for 3 seconds. They will then be asked to sit down on

the chair at their own comfortable speed and maintain this position for 3 seconds. Each subject will repeat the movements 3 times, and the mean data will be used for statistical analysis. Asymptomatic participants will serve as a control group in the first assessment in order to detect differences in kinematic parameters during STS and its reverse between the CNLBP patients and asymptomatic participants. Hence, they will not participate in the intervention phase and the second assessment (Figure 1).

Following the assessment, CNLBP participants will be randomly divided into 2 groups (core stabilization exercise and general exercise) for treatment. First, all CNLBP participants will perform warm-up exercises that consist of 8 stretching exercises (hamstrings, quadriceps, latissimus dorsi, and iliotibial band of both sides; 1 set of 5 repetitions with a 10-second hold per repetition) and stationary bicycling for a period of 10 minutes [37,38]. Based on the previous recommendations, a staged approach will be followed for both groups [38] (see Multimedia Appendix 1). This approach includes 8 exercise levels with progressively increasing difficulty [38]. In the first session, the exercises will be explained and demonstrated to CNLBP participants. We will try to use the Template for Intervention Description and Replication checklist [39] as a guideline to improve the completeness of reporting of our intervention procedure.

Figure 1. CONSORT diagram illustrating flow of participants through the COSCIOUS.



Core Stabilization Exercise

Core stabilization or motor control exercise is a common type of therapeutic exercises prescribed for LBP patients. Core stabilization exercise is designed to re-educate the coactivation pattern of abdominals, paraspinals, gluteals, pelvic floor muscles, and diaphragm [23,40]. The biological rationale for core stabilization exercise is primarily based on the idea that the stability and control of the spine are altered in patients with LBP [41]. A core stabilization exercise program begins with recognition of the natural position of the spine (midrange between lumbar flexion and extension ROM), considered to be the position of balance and power for improving performance in various sports [42]. Initial low-level sustained isometric contraction of trunk stabilizing muscles and their progressive integration into functional tasks is the requirement of core stabilization exercise [21]. To ensure correct activation of the transversus abdominis muscle, it will be emphasized to CNLBP participants that the lower part of the anterior abdominal wall below the umbilical level needs to be "drawn in" during contraction of this muscle. Furthermore, bulging action of the multifidus muscle needs to be felt under the physical therapist's fingers when they are placed on either side of the spinous processes of the L4 and L5 lumbar vertebral levels, directly over the belly of the muscle [37]. Participants will be made aware of and will be told to avoid incorrect muscle activation (substitution strategies).

General Exercise

General exercise is an umbrella term that can involve strengthening exercise for all the main muscle groups with or without the addition of weights [43]. In addition, this umbrella term can consist of exercises improving coordination, stretching, and aerobic fitness training [43]. In our study, exercises activating the extensor (paraspinals) and flexor (abdominals) muscle groups will be performed in a lying position initiating

with simple movements and progressing to more difficult exercises (eg, on a gym ball).

The same frequency (*3 times per week*; Saturday, Monday, Wednesday) and duration (6 weeks; 16 sessions) will be provided for both groups [37]. All treatment sessions will be held in the morning (8 AM to 12 PM). In each session, participants will be instructed to perform their exercises as many times as they can with rest periods in the same session. However, the holding time and number of contractions will be progressively increased up to 10 contraction repetitions × 10 second duration each [38]. Finally, exercise sets will be increased from 3 to 5 sets. The first session will last for 30 to 45 minutes, and the time of treatment session will be gradually increased in a dose-dependent manner. Based on Koumantakis et al [38] study, CNLBP participants in the core stabilization exercise group will be asked to activate their muscles at about 30% of their maximum activation level during the performance of stabilization exercises, and CNLBP participants in the general exercise group will be asked to activate their muscles at about 60% to 70% during the performance of general exercises. However, in the core stabilization exercise group, heavier load functional tasks, with exercises similar to those conducted by CNLBP participants in the general exercise group, will be progressively introduced in the last 6 sessions of the program [37]. All exercises will be performed under supervision of an experienced physical therapist. Moreover, to control confounding variables and create a standard and homogeneous condition for all CNLBP participants, they will be instructed not to perform exercises at home between the treatment sessions. Treating physical therapist will explain the positive effects of exercise on health in each session to improve adherence of CNLBP participants to intervention protocol. Any deviations from the exercise protocol, such as the receipt of any additional interventions or therapy for LBP, will be recorded and the decision will be made on whether the participant should be excluded from the study.

After 16 treatment sessions, all CNLBP participants will be evaluated again in the same manner as the initial assessment. Pain intensity and functional disability will be measured using the VAS and the Persian translated version of the RMDQ. Figure 1 illustrates a Consolidated Standards of Reporting Trials (CONSORT) diagram of this study.

Management of Adverse Events

CNLBP participants will be encouraged to contact their treating physical therapist between appointments if they have any concerns about their exercise program or if they experience an increase in pain. These concerns will be addressed by their treating physical therapist and details of the issue and outcome recorded [44]. Any adverse events will be recorded and reported to the ethics committee at Iran University of Medical Sciences.

Main Outcome Measures

Kinematic Analysis

The maximum flexion and extension ROM, the timing of their occurrence, and angular velocities of the lumbar spine and right and left hips will be computed in asymptomatic and CNLBP participants during flexion and extension phases [12] of STS and its reverse. The ratios of the total movements of the lumbar spine to those of the right hip and to the left hip will be determined during STS movement and its reverse. These ratios indicate the relative contributions of the joint pairs throughout the ROM. These kinematic parameters will be assessed again in both intervention groups after intervention. Each STS and its reverse will be screened to determine visually the beginning and the end of the movement. A single investigator will follow the same rule for every participant; start of T12 anterior displacement and stop of S2 displacement. Sagittal lumbar and hip angles will be calculated following filtering of the raw data using a robust low-pass Butterworth filter (6 Hz) [45].

Relative Phase Angle Analysis

Relative phase angle (RPA) is considered a technique to quantify coordination patterns and variability in the dynamical systems theory approach [46]. The RPA can represent both temporal and spatial information continuously throughout the STS movement and its reverse [46]. The RPA will be used to measure interjoint coordination between the lumbar spine and dominant hip. Phase angle is defined as the inverse tangent of angular velocity/angular displacement and will be calculated for each data point through the entire cycle (phase angle $\phi \tan^{-1}$ [angular velocity/angular displacement]). The RPA between 2 body segments, which represents the joint coordination, will be calculated continuously from the differences between the phase angles of 2 joints (dominant hip–lumbar spine) [12,46]. The dominant leg will be determined by asking the participants with which leg they prefer to kick a ball [47]. If the RPA is negative, the hip is lagging the lumbar spine, and if the phase difference is positive, the hip movement is leading the lumbar spine [12]. Maximum and minimum relative phase differences and their timing will be computed before and after intervention in CNLBP participants. Furthermore, the relative phase relationship between the lumbar spine and hips (relative phase difference; x-axis) versus each percent of movement (y-axis) for STS and its reverse will be displayed in plots before and after intervention.

Statistical Analysis

Statistical analyses will be performed on a personal laptop using SPSS for Windows release version 21.0 (IBM Corp) and STATA version 13 (StataCorp LLC). The comparability of asymptomatic participants and CNLBP patients on disability level, pain intensity, and kinematic variables at baseline will be analyzed using the independent *t* tests for parametric and Wilcoxon test for nonparametric distribution. In addition, a mixed-model 2-way analysis of variance (ANOVA) for each dependent variable (disability level, pain intensity, maximum joints ROM, joint angular velocities, lumbar/hip motion ratios, and maximum and minimum relative phase differences), with the 2 factors being group (core stabilization/general exercise) and time (preintervention/postintervention). After intervention, comparison between core stabilization group, general exercise group, and asymptomatic participants will be made using the ANOVA test (*Scheffe* post hoc tests). In addition, an intention-to-treat analysis will be conducted if any protocol deviation is observed at the end of the study due to attrition or loss to follow-up. Perceived pain and functional disability will

be compared with consensus standards for minimal clinically important change (MCIC) [48]. Ostelo et al [48] considered the MCIC for VAS as 15 mm and for RMDQ as 5 points for patients with LBP. Furthermore, effects sizes will be measured using the Cohen *d* [49]. Statistical significance level is set at $P \leq .05$.

Results

COSCIOUS should be completed in December 2017. The results of this study will be submitted to a peer-reviewed MEDLINE-indexed journal for publication and will be presented at national and international academic and clinical conferences.

Discussion

Overview

To the best of the authors' knowledge, this is the first time an investigation will evaluate the effects of core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with CNLBP. STS movement and its reverse are important functions required for conducting activities of daily living. Previous study has shown that these skills would be impaired in acute LBP [12]. However, the effects of CNLBP on flexion and extension phases of STS and its reverse is not well known, and COSCIOUS aims to investigate this issue.

Physical therapy programs play a key role in multimodal treatment approaches for CNLBP [50]. Therapeutic exercise is one of the few clearly effective physical therapy treatments to relieve pain for adults with CNLBP [50,51]. The European guidelines for the management of CNLBP suggest supervised exercise therapy as a first-line treatment [52]. In this investigation, the effect of the 2 most common types of therapeutic exercises prescribed for patients with LBP will be evaluated on the kinematics and joint coordination of functionally important activities. To the best of authors' knowledge, no published study has assessed the effect of exercise therapy on STS movement and its reverse. The main study question is whether core stabilization exercise programs are effective in improving kinematic variables during STS and its reverse in CNLBP. In addition, a comparison will be made between the results of the 2 therapeutic exercises on STS and its reverse. The results of COSCIOUS will provide some insight into the effects of CNLBP on lumbar spine–hip coordination of activities of daily living.

Limitations

The main limitation of this study is that young and middle-aged CNLBP participants will be included, thereby, the generalizability is limited. In addition, some study participants may be lost to follow-up.

Conclusion

COSCIOUS will evaluate the effects of core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during STS and its reverse in patients with CNLBP. In addition, the effects of CNLBP on the STS and its reverse will be investigated.

Acknowledgments

We would like to thank the personnel of the biomechanics laboratory and physical therapy clinic at the School of Rehabilitation Sciences, Iran University of Medical Sciences (Tehran, Iran) for their cooperation.

Authors' Contributions

MRP, IET, SJ, and MAS are responsible for the design of the study and managed literature searches. RB and MT helped in the methodological considerations, and HM and JS helped in the design, methodological considerations, and English editing of the manuscript. MRP, IET, and MAS led the statistical analysis. MRP wrote the first draft and the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Core stabilization and general exercise programs.

[PDF File (Adobe PDF File), 852KB - resprot_v6i6e109_app1.pdf]

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Abbreviations

ANOVA: analysis of variance
ASIS: anterior superior iliac spine
CLBP: chronic low back pain
CNLBP: chronic nonspecific low back pain
COM: center of mass
CONSORT: Consolidated Standards of Reporting Trials
COSCIOUS: core stabilization exercise on the kinematics and joint coordination of the lumbar spine and hip during sit-to-stand and its reverse in patients with chronic nonspecific low back pain
LBP: low back pain
LH: left hip
MCIC: minimal clinically important change
PSIS: posterior superior iliac spine
QTM: Qualisys track manager
RH: right hip
RMDQ: Ronald-Morris Disability Questionnaire
ROM: range of motion
RPA: relative phase angle
STS: sit-to-stand
VAS: visual analog scale

Edited by G Eysenbach; submitted 04.03.17; peer-reviewed by M Shafizadeh; comments to author 14.04.17; revised version received 30.04.17; accepted 02.05.17; published 01.06.17.

Please cite as:
Pourahmadi MR, Ebrahimi Takamjani I, Jaberzadeh S, Sarrafzadeh J, Sanjari MA, Mohsenifar H, Bagheri R, Taghipour M
The Effect of Core Stabilization Exercise on the Kinematics and Joint Coordination of the Lumbar Spine and Hip During Sit-to-Stand and Stand-to-Sit in Patients With Chronic Nonspecific Low Back Pain (COSCIOUS): Study Protocol for a Randomized Double-Blind Controlled Trial
JMIR Res Protoc 2017;6(6):e109
URL: http://www.researchprotocols.org/2017/6/e109/
doi:10.2196/resprot.7378
PMID:28572078

Protocol

Pain Improvement With Novel Combination Analgesic Regimens (PAIN-CARE): Randomized Controlled Trial Protocol

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Abstract

Background: Neuropathic pain (NP) (including painful diabetic neuropathy, postherpetic neuralgia, etc) affects approximately 7% to 8% of the population and is associated with a devastating symptom burden as well as a profound economic impact for patients, their families, and the health care system. Current therapies have limited efficacy and dose-limiting adverse effects (AEs). Rational combination therapy with carefully selected NP drugs has shown potential for measurable improvements in pain relief, quality of life, and health care use. Today, over half of NP patients concurrently receive 2 or more analgesics but combination use is based on little evidence. Research is urgently needed to identify safer, more effective combinations.

Objective: We hypothesize that analgesic combinations containing at least 1 nonsedating agent would be as safe but more effective than either monotherapy without increasing overall AEs because of additive pain relief. Pregabalin (PGB), a sedating anticonvulsant, is proven effective for NP; the antioxidant alpha-lipoic acid (ALA) is one of the only nonsedating systemic agents proven effective for NP. Thus, we will conduct a clinical trial to compare a PGB+ALA combination to each monotherapy for NP.

Methods: Using a double-blind, double-dummy, crossover design, 54 adults with NP will be randomly allocated to 1 of 6 sequences of treatment with PGB, ALA and PGB+ALA combination. During each of 3 different treatment periods, participants will take 2 sets of capsules containing (1) ALA or placebo and (2) PGB or placebo for 31 days, followed by an 11-day taper/washout period. The primary outcome will be mean daily pain intensity (0-10) at maximally tolerated dose (MTD) during each period. Secondary outcomes, assessed at MTD, will include global improvement, adverse events, mood, and quality of life.

Results: Participant recruitment is expected to begin September 1, 2017. The proposed trial was awarded external peer-reviewed funding by the Canadian Institutes of Health Research (Canada) on July 15, 2016.

Conclusions: This trial will provide rigorous evidence comparing the efficacy of a PGB+ALA combination to PGB alone and ALA alone in the treatment of NP.

Trial Registration: International Standard Randomized Controlled Trial Number ISRCTN14577546; http://www.isrctn.com/ISRCTN14577546?q=&filters=conditionCategory:Signs%20and%20Symptoms,trialStatus:Ongoing,recruitmentCountry:Canada&sort=&offset=1&totalResults=2&page=1&pageSize=10&searchType=basic-search (Archived by WebCite at http://www.webcitation.org/6qvHFDc6m)

(JMIR Res Protoc 2017;6(6):e111) doi:10.2196/resprot.7493

KEYWORDS

neuropathic pain; alpha-lipoic acid; antioxidant; pregabalin; anticonvulsant

Introduction

Chronic pain has a prevalence of 20% to 25% [1] and is one of the most frequent reasons to seek health care and miss work [2]. Pain impairs physical, social, and occupational function and thus exerts a devastating impact on patients, their families, and society. Each year in North America, chronic pain costs over $650 billion in health care and lost productivity thus exceeding costs of heart disease, cancer, and diabetes [3]. Neuropathic pain (NP) is a common form of chronic pain caused by nervous system diseases [4,5] including radiculopathy, diabetic neuropathy, HIV-neuropathy, and cancer-related NP [6]. NP is more prevalent in the elderly and we need to prioritize treatment research as our population ages [7]. NP management involves treating underlying causes, reducing pain, and improving function. Systemic oral pharmacotherapy is a valuable component of multimodal NP management [8] given ease of administration and engagement of drug effect sites throughout the sensory nervous system. However, current treatments give only partial benefit due to incomplete efficacy and dose-limiting adverse effects (AEs) [8]. In addition to reversible AEs such as sedation, excessive pain-contingent dosing of drugs with incomplete efficacy can lead to catastrophic outcomes such as opioid-related [9] and anti-inflammatory drug (NSAID)–related toxicity and death [10].

Due to perceived benefits of combination therapy [11,12], more than 50% of NP patients concurrently receive 2 or more analgesics [13]. However, current combination prescribing is based on little evidence, some combinations may be harmful, and authorities have demanded more research to develop rational combination strategies [8]. This field has received little attention from industry, emphasizing the need for public funding. Rational combination therapy with mechanistically different agents has shown potential for measurable improvements in pain relief, quality of life, and health care utilization and, indirectly, fewer NSAID-related and opioid-related mortalities. Combination therapy has been studied in many therapeutic areas but only recently in NP. Although our previous trials [14-16] support the merits of combination therapy, other data indicate that some combinations confer no benefit in some conditions [17] and other combinations do more harm than good [18]. Our Cochrane review [11] identified only 21 NP trials of different combinations. This dearth of evidence emphasizes the urgent need for more research.

A combination of pregabalin (PGB, Lyrica) plus alpha-lipoic acid (ALA) is now the most important to study because (1) high-quality evidence supports the efficacy of these agents as monotherapies in NP; (2) ALA is inexpensive, widely accessible, and currently the only nonsedating systemic agent for NP [19]; (3) PGB also improves sleep, mood, and anxiety [20]; (4) PGB and ALA have complementary mechanisms providing the expectation of greater synergy; and (5) AE profiles are different and combining PGB+ALA will not increase overall AEs. Combining a sedating and nonsedating agent is a novel approach with vast potential for improved patient outcomes. This project directly addresses a desperate need to improve chronic pain treatment.

Both PGB and ALA are approved by Health Canada for clinical use and proven for the treatment of NP [8,19]. PGB blocks the α-2-δ subunit of N-type voltage gated calcium channels, resulting in decreased calcium influx and neurotransmitter release [21,22]. PGB is recommended as first-line treatment for NP [8], and a recent meta-analysis of 19 trials (7003 participants) yielded a number-needed-to-treat (NNT for 50% pain reduction) of 5.0 for NP [20]. AEs (at 600 mg per day) included sedation (15%-25%) and dizziness (27%-46%). Our experience with PGB includes a Pfizer-sponsored trial [23] and, more recently, an investigator-initiated trial of PGB plus duloxetine for fibromyalgia [24]. ALA has been extensively studied in NP, and its therapeutic effects in this setting appear to be, in part, due to its antioxidant actions [25]. In a rat model of streptozocin-induced diabetes, ALA delayed the onset of polyneuropathy [26]. Mechanistic studies suggest decreased nociceptive sensitivity by inhibition of T-type calcium (Cav3.2) channels [27], distinct from that of PGB, which inhibits N-type calcium channels [22], suggesting potential for synergy at these different sites of action. At least 16 trials of over 1320 patients have reported reductions in pain and other symptoms [19,28], and a recent meta-analysis reported an NNT of 6.3 [19]. Also, 1 trial reported improvement in NP symptoms after 4 years of treatment [29]. AEs of nausea, vomiting, headache, and vertigo have been reported in studies involving more than 1200 mg per day of ALA. There have also been rare reports of hypoglycemia (low blood sugar) in diabetic patients taking ALA and reporting symptoms of sweating, paleness, chills, headache, dizziness, and confusion. We identified only 1 study of a combination similar to PGB+ALA—ALA plus gabapentin (related to PGB) in the treatment of burning mouth syndrome [30]. Despite major methodological flaws, the study suggested greater benefit with this combination versus monotherapy, and AEs were reported overall as very mild [30].

Thus, our objective is to conduct an innovative double-blind, randomized controlled trial (RCT) to compare a combination of the anticonvulsant PGB with the nonsedating antioxidant ALA to each monotherapy in NP.

Methods

Ethics

This study underwent ethics review and received a compliance notice by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board on December 15, 2016. This trial will be conducted at one site, Providence Care Centre, Kingston, Ontario, Canada.

Aims and Hypothesis

The objective of this trial is to compare the safety and efficacy of a PGB+ALA combination to each monotherapy in treating participants with NP. Our primary hypothesis is that PGB+ALA has greater analgesic efficacy versus either monotherapy.

Trial Design

We have designed a single center double-blind, double-dummy, randomized, controlled, 3-period crossover trial (compliant with Health Canada; International Conference on Harmonization; Methods, Measurement, and Pain Assessment in Clinical Trials; and Consolidated Standards of Reporting Trials [CONSORT]) comparing a PGB+ALA combination to monotherapy in treating NP (Figures 1 and 2). Using a flexible dose titration, Latin Square crossover design, treatments will be titrated during each of 3 treatment periods to maximal tolerated dose (MTD) with primary and secondary trial analyses comparing the 3 treatments using end-of-period outcomes. Given ethical issues and since PGB and ALA are proven with multiple trials confirming superiority over placebo [19,20], this active control superiority design does not include a placebo alone treatment. Furthermore, our previous trials [14-16] have confirmed assay sensitivity with a similar design. Internal validity of our crossover design is supported by stability of NP over time [14-17,31] and the risk of carryover from one period to the next is very low because each period is followed by an 11-day dose taper and drug washout, and the final MTD week for each period (from which the primary outcome is obtained) is separated from the next period's final week by 7 weeks (ie, ≥20 half-lives of the drugs studied). Nevertheless, exploratory analyses will be conducted to identify if any low-order carryover effect does exist.

During each of 3 trial periods, using a double-blind randomized crossover design, patients will receive 2 sets of capsules (Figure 3): (1) blue capsules (ALA 300 mg or placebo) and (2) gray capsules (PGB 75 mg or placebo). During the combination period, blue will contain ALA and gray will contain PGB. During the ALA alone period, blue will contain ALA and gray will contain placebo. During the PGB alone period, blue will contain placebo and gray will contain PGB.

Consenting patients on ALA or PGB (or gabapentin) pretrial will agree to be weaned gradually for a washout of at least 7 days. Patients taking and perceiving benefit from opioids (<90 mg morphine equivalents), antidepressants (tricyclic, selective serotonin reuptake inhibitor, or serotonin–norepinephrine reuptake inhibitor), NSAIDs, or acetaminophen may continue these at a steady dose for the entire study. Any cognitive behavioral therapy or exercise programs may continue only if they can be scheduled evenly across all treatment periods. Research staff will monitor and advise patients weekly about prohibited cointerventions throughout the study. A thorough understanding of the threats to validity of using forbidden cointerventions is heavily emphasized to participants. Patients will not be allowed to start new cognitive behavioral therapy or exercise programs after study initiation and must avoid any procedural therapies (eg, nerve blocks or acupuncture) during the entire study. Any pain exacerbations that in the opinion of the patient warrant initiation of a new therapy would necessitate trial discontinuation and immediate weaning from study medications, but these patients would still be included in the trial analyses.

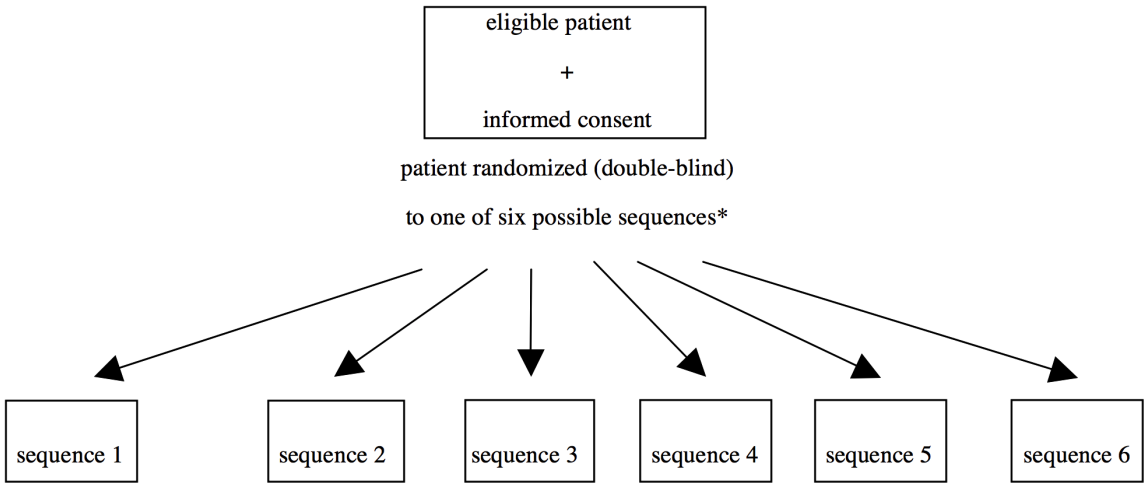
Dose Titration

Study medication will follow a flexible dose titration to MTD to balance tolerability and relief, with regular weekly calls by research personnel. This means that doses of study medication will not be further increased if intolerable AEs are encountered at higher doses or if "a lot" or "complete" pain relief is achieved. If AEs are experienced subsequent to a dose increase of study medications, the protocol will allow for dose reduction to the previous dosage level in order to improve tolerability. The MTD fixed dose week will be from days 25 to 31. However, if MTD is reached before day 25, that MTD dose will continue up to and including the day 25 to 31 period. For ALA, the maximum possible daily dose will be 1800 mg, and for PGB the maximum possible daily dose will be 450 mg. The MTD fixed dose week will be followed by a 7-day dose taper and 4-day complete washout. Daily pain ratings will be completed throughout the trial. During dose taper and washout periods only, patients may take acetaminophen, ≤8 tablets per day (325 mg per tablet) as needed. This rescue medication is very unlikely to affect the primary outcome measure of pain intensity during the MTD phase of each treatment period.

Participant Allocation

As per the 3-period Latin Square crossover, patients are randomly allocated to 1 of 6 sequences of ALA, PGB, and combination (Figure 1). Before the trial, an independent pharmacist and biostatistician will prepare a concealed allocation schedule using a computer-generated block randomization process to randomly assign treatment sequences to a consecutive series of numbers within a block. Each patient will be assigned to the next consecutive number, and the corresponding sequence of medications will be dispensed. All study personnel will be blinded to the block sizes to preserve allocation concealment.

Figure 1. Trial design.



This will each be a 3-period, active treatment-controlled randomized double-blind trial, using a double-dummy, balanced Latin Square crossover design in which patients will be allocated to one of 6 treatment sequences of the three treatments: ALA, PGB and ALA-PGB combination

*see below for specific treatment sequences

TREATMENT SEQUENCES

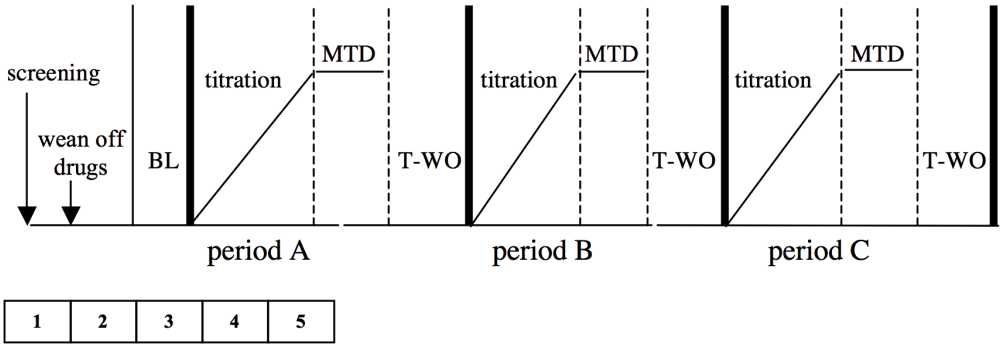
(each patient is randomized to ONE of these sequences)

[All patients complete all three treatment periods (i.e. A, B and C) as per the treatment sequence they were randomized to (i.e. 1, 2, 3, 4, 5 or 6)]

Baseline 7 day washout of prohibited medications (e.g. gabapentin, pregabalin, alpha-lipoic acid)	Sequence	A 8 weeks (24 day titration; 7 day fixed; 7 day taper; 4 day washout)	B 8 weeks (24 day titration; 7 day fixed; 7 day taper; 4 day washout)	C 8 weeks (24 day titration; 7 day fixed; 7 day taper; 4 day washout)
	1	COMBINATION (A + P)	Alpha-lipoic acid (A+ Pp)	PREGABALIN (Pa + P)
	2	PREGABALIN (Pa + P)	COMBINATION (A + P)	Alpha-lipoic acid (A + Pp)
	3	Alpha-lipoic acid (A + Pp)	PREGABALIN (Pa + P)	COMBINATION (A + P)
	4	COMBINATION (A + P)	PREGABALIN (Pa + P)	Alpha-lipoic acid (A+ Pp)
	5	PREGABALIN (Pa + P)	Alpha-lipoic acid (A + Pp)	COMBINATION (A + P)
	6	Alpha-lipoic acid (A + Pp)	COMBINATION (A + P)	PREGABALIN (Pa + P)

Legend: Symbols in parentheses indicate the content of the corresponding blinded study drug capsules as per the double-dummy design. A=alpha-lipoic acid; Pa= “alpha-lipoic acid” placebo; P=pregabalin; Pp= “pregabalin” placebo

Figure 2. Trial design, continued.



LEGEND:

1. Screening

2. Wean off current alpha-lipoic acid, gabapentin and pregabalin for ≥1 week prior to commencing

   - patients taking, and perceiving benefit from opioids (<90/day morphine equivalents), antidepressants, nonsteroidal anti-inflammatory agents or acetaminophen may continue these at a steady dose during the study.

   - patients required to avoid any procedural pain therapies (e.g. neurosurgical interventions, nerve blocks or acupuncture) during the entire study as these treatments may be unevenly distributed across treatment periods and could skew the study's results.

3. BL – 7 day baseline period

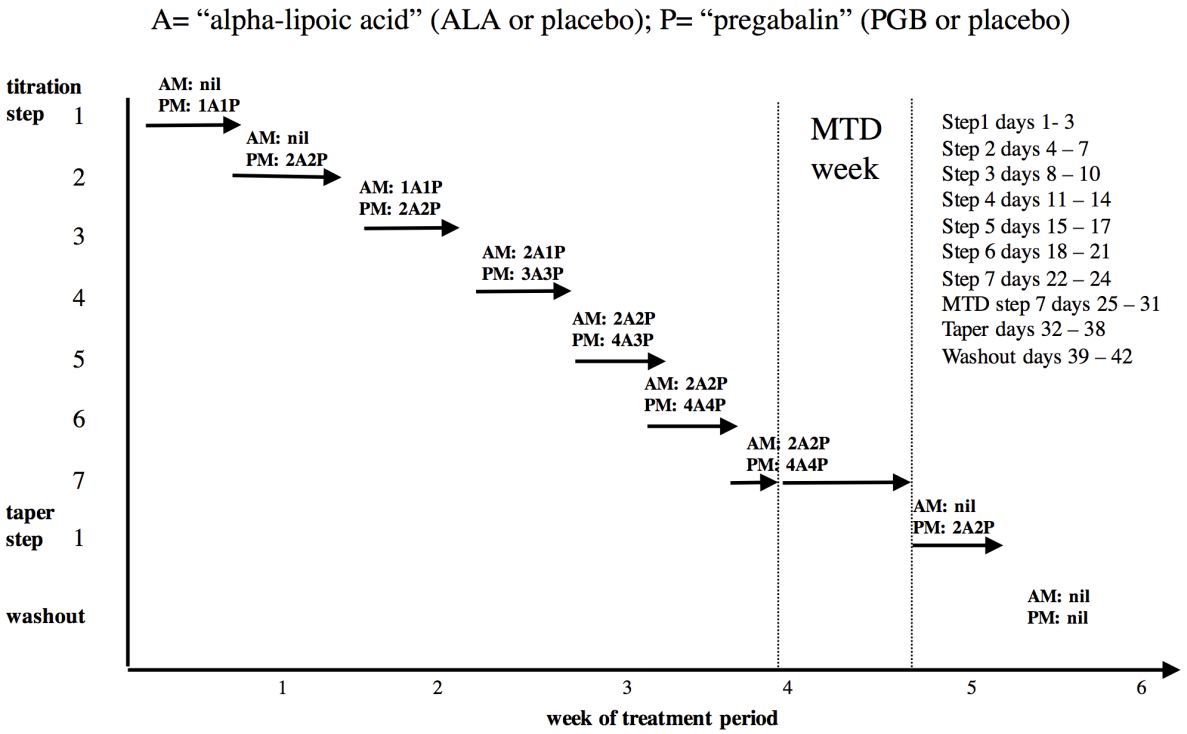
4. Double-blind randomization to one of six possible treatment sequences (e.g. sequence 1: combination>alpha-lipoic acid>pregabalin) such that each patient progresses through each of three 6 week treatment periods (i.e. periods “A”, “B” and “C”).

5. Each treatment period starts with a 24 day study drug dose titration towards maximal tolerated dose (MTD). If MTD is reached before the end of this 24 day period, that dose will be continued up to and including days 25-31 of the treatment period and then concluded with a 7 day taper/ 4 day washout (T-WO).

   A study nurse will contact patients by telephone at least twice a week to evaluate adverse effects, guide study drug titration and encourage compliance. Study patients will be encouraged to contact a study physician, as needed, who will be available 24 hours a day by pager in order to deal with study-related problems that may occur between scheduled study nurse telephone calls.

   With each dosage increase of study medication in the titration schedule, if mild to moderate treatment-emergent adverse effects are encountered, patients will be asked if they can tolerate continuing at that dose for another 2-3 days. If so, this dosage will be continued with the expectation that tolerance to side effects will occur. If side effects are intolerable or do not improve, both study medications will be decreased to the next lowest possible dose and an increase will be attempted one more time at the next scheduled dose increase. If this again results in intolerable side effects, both study drugs will be decrease back to the previous dose, which will be defined as the maximally tolerated dose (MTD) for that individual.

Figure 3. Study drug schedules.



For each trial period, patients receive blue “A” (ALA 300 or placebo), and grey “P” (PGB 75mg or placebo), capsules. Each step above indicates the number of each capsules taken before breakfast & in the evening. The schedule above indicates uppermost dose ceilings at each timepoint. Titration towards individual maximally tolerated dose (MTD) will be guided by safety determined by weekly AE monitoring. Thus, titration may be slower and MTD may be lower than shown above.

Protecting Against Bias

Medications will be encapsulated (ALA, blue; PGB, gray) in an identical fashion across all periods. As per a double-blind, double-dummy design, patients will take both sets of medications so all treatment conditions will be identical across all 3 treatment periods. Treatment codes will be generated by the investigational pharmacist and concealed until trial completion. In case of emergency, individual codes will be disclosed by an investigational pharmacist to a nonstudy clinician. A questionnaire completed by every participant at the end of each period will ask patients to guess the treatment they received to assess blinding.

Inclusion and Exclusion Criteria

With the input of longstanding specialist and primary care colleagues in the Kingston and Queen’s University catchment area, men and women meeting the diagnostic criteria for peripheral NP will be considered for the trial. Participants must have a score of 3 or higher on the Douleur Neuropathique 4 interview, a validated questionnaire that distinguishes between neuropathic and nonneuropathic pain [32]. As indicated, investigations will be done to confirm NP diagnosis including, but not limited to, nerve conduction studies and electromyography. After preliminary phone screening, candidates will be invited to the clinic for a detailed history, physical, neurological examination, and a review of recent (within the last 3 months) lab studies including complete blood count, glucose, electrolytes, urea, creatinine, aspartate transaminase and alanine transaminase (AST/ALT), glycosylated hemoglobin, and electrocardiogram. Laboratory analysis will be conducted for study candidates with no recent records. Eligible patients will have daily pain (≥3/10) for at least 3 months, AST/ALT ≤120% upper limit of normal, creatinine clearance ≥60 mL per minute, and glycosylated hemoglobin ≤9.5%. Patients will have necessary abilities, visual acuity, and language skills for questionnaire completion and phone communication with nurses. Patients with major organ system disease, cardiovascular autonomic neuropathy, moderate to severe sedation or ataxia due to other required drugs, hypersensitivity to study medications, seizure disorder, or other painful condition >50% as severe as their NP will be excluded. Patients with a major, poorly controlled psychiatric disorder, severe depression or suicidal ideation, or active substance abuse disorder will be excluded. Patients with a history of angioedema will be excluded. Those who live alone and cannot assure daily

contact with a friend, family member, or caregiver will be excluded. Women of childbearing potential will be required to receive a highly effective form of contraception (total abstinence, hormonal birth control methods, intrauterine devices, confirmed successful vasectomy of partner, double barrier methods, etc) and a negative pregnancy test at baseline. If a study participant becomes pregnant, she must stop using study medications immediately and will be withdrawn from the study. Eligible patients will be enrolled into the study following informed consent.

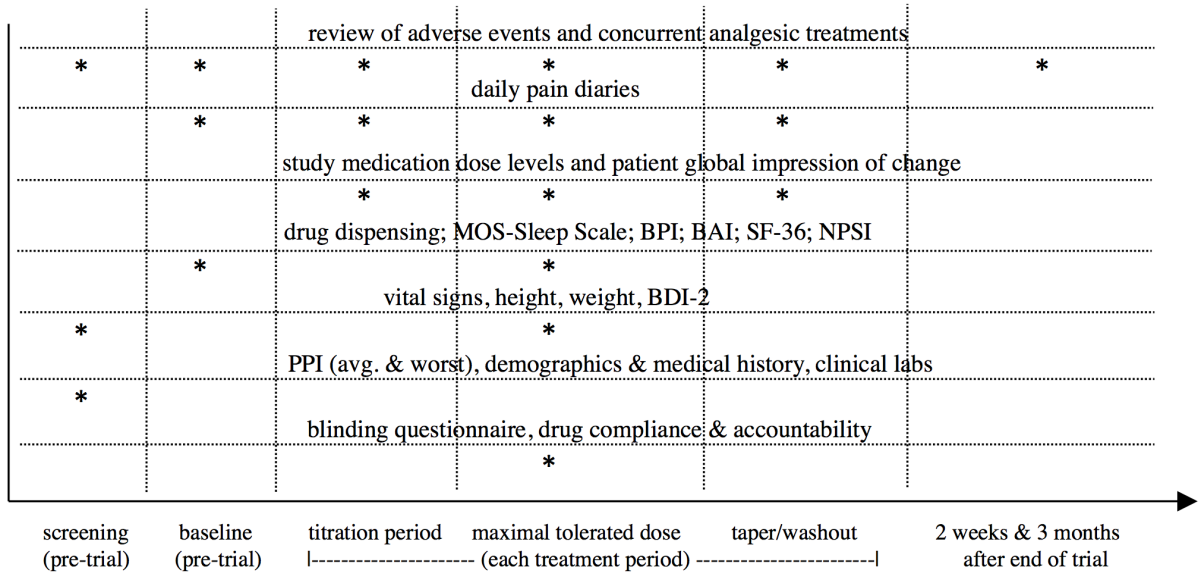
Trial Duration and Follow-Up Frequency

Each of the 3 treatment periods will be 6 weeks, for a total trial duration of 18 weeks. The nurse will phone patients weekly to evaluate AEs, guide drug titration, and encourage compliance. Patients will be seen in the clinic at the end of each treatment period for assessment of vital signs and measurement of secondary outcomes (Figure 4). Patients will be followed up by phone 2 weeks and 3 months after trial completion (including patients who were withdrawn from the trial prematurely) to document any subsequent AEs.

Outcome Measures and Safety Assessment

The primary outcome is mean daily pain (0-10 numerical rating scale with 0 = no pain, 10 = worst pain imaginable) averaged over the MTD fixed dose week (days 25-31) of each period (Figure 4). Secondary outcomes include daily pain at other time points, the MTDs of PGB and ALA, frequency and severity of AEs and global relief, the short form McGill Pain Questionnaire [33], the Neuropathic Pain Symptom Inventory [34], the Brief Pain Inventory [35], the Beck Depression Inventory-II [36], Beck Anxiety Inventory [37], the Short Form survey (SF-36) [38], blinding questionnaires, and acetaminophen consumption. Timing of outcome assessments is described in Figure 4. Patient safety will be ensured by vigilant AE assessment and judicious drug titration. Any occurrences of major AEs will be tracked as secondary outcomes and also reported to the Queen's Ethics Board, Health Canada. Assessment and reporting of AEs will adhere to CONSORT recommendations [39].

Figure 4. Schedule of assessments.



PPI – present pain intensity (0-10 numerical scale)
MOS – Medical Outcomes Study
SF-MPQ – short form McGill Pain Questionnaire;
BPI – Brief Pain Inventory;
† Blood sample at baseline for genetic analyses

BDI-2 – Beck Depression Inventory - 2;
BAI – Beck Anxiety Inventory;
SF-36 – the MOS 36-item short-form health survey
NPSI – neuropathic pain symptom inventory

Sample Size

Based on previous estimates of within-patient variation, variance=2.3, from our previous study in NP [15], we calculate that a sample of 55 trial completers would provide an 80% chance of detecting (alpha=0.05) a mean treatment difference of 1 point (0-10 scale). For a sample size divisible by 6, the number of treatment sequences, we adjusted the sample size to 54 trial completers.

Statistical Analyses

Analyses for this trial are based on the null hypothesis of no difference between PGB, ALA, and PGB+ALA and the alternative hypothesis that at least 2 treatments are different. When a patient contributes data from only one period, sensitivity analyses including all patients will also be performed by assuming some reasonable but extreme values for the remaining periods. All patients receiving at least one dose of drug will be included in the safety analyses.

The primary outcome—mean daily pain from the last 7 days (at MTD) of each treatment period—will be calculated as an average of pain scores as recorded in the pain diary if more than 50% of the information (ie, at least 4 days) is not missing. Otherwise, mean daily pain will be treated as missing. This is based on the half rule often used to summarize repeated responses and which has proven unlikely to introduce bias to trial results [40]. Sensitivity analyses based on the average of all available pain scores will also be performed to confirm the results of the primary analysis. Although carryover effects are unlikely, we recognize this possibility. Therefore, a linear mixed model with sequence, period, treatment, and the first order carryover term as fixed effects and patient as a random effect [41] will be used to test for differences among the 3 treatments and to estimate the least square mean of the mean daily pain intensity for each treatment, adjusting for carryover as well as period effects (ie, stability of pain levels). The following 3 pair-wise comparisons will be performed based on the least square means and standard deviations from the linear mixed model: combination versus ALA alone, combination versus PGB alone, and ALA alone versus PGB alone. Sensitivity analyses will be performed using a pattern-mixture model [42] based on patterns of missing data so as to check the robustness of results in the case that data may not be missing at random. A Fisher's least significant difference [43] procedure will be used to adjust the *P* values for these 3 comparisons.

Secondary outcomes will be analyzed similarly except that (1) only one measurement is analyzed in the last week for the singular measures (ie, final week questionnaires) and (2) the scoring algorithms developed for the Brief Pain Inventory, Beck Depression Inventory-II, and SF-36 will be first used to derive the subscales or domains within these instruments, and the scores on these subscales or domains will be used as response variables in the linear mixed model analysis.

Results

Participant recruitment is expected to begin September 1, 2017. The proposed trial was awarded external peer-reviewed funding by the Canadian Institutes of Health Research (Canada) on July 15, 2016.

Discussion

NP remains a challenging condition to treat, with current analgesic drugs providing only partial relief, often at the risk of disabling AEs. To the best of our knowledge, this proposed trial is the first to compare the combination of an anticonvulsant with an antioxidant to treat NP. Because ALA and PGB have different AE profiles, we expect their combination to provide superior analgesic efficacy in NP without increasing AEs.

Potential threats to completing this trial include challenges with participant enrollment, noncompliance, protocol violations, and early dropouts. However, we are confident that the proposed trial design and our experience with recent and previous RCTs will minimize these concerns. Also, noncompliance, protocol violations, and early dropouts will be minimized by the crossover design as well as thorough patient teaching and careful follow-up of trial patients.

As discussed above, there is an urgent need for improved NP treatments with better analgesic efficacy and better safety and tolerability. Thus, this trial shall provide rigorous evidence for a potentially improved treatment strategy for NP.

Acknowledgments

The authors thank the Canadian Institutes of Health Research and the Queen’s University Department of Anesthesiology and Perioperative Medicine.

Authors' Contributions

IG led the writing of this manuscript and the development of this protocol. DT led the development of the statistical analysis plan and contributed to writing of this manuscript and the development of the protocol. RRH participated in the writing of this manuscript and the initial protocol development, including selection of mood and quality of life measures. ACJ and NG participated in the initial protocol development. SD, EV, and RM participated in the writing of this manuscript and the initial protocol development. All authors read and approved the manuscript. All authors will be involved in data analysis and interpretation and future manuscript preparation.

Conflicts of Interest

IG has received support from Adynxx, TARIS Biomedical, AstraZeneca, Pfizer, and Johnson and Johnson and has received grants from the Canadian Institutes of Health Research, Physicians’ Services Incorporated Foundation, and Queen’s University. RRH has received research funding from the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council of Canada, the American Foundation for Suicide Prevention, and Queen’s University. ACJ has received grants from the Canadian Institutes of Health Research, Research Manitoba (formerly the Manitoba Health Research Council), and the University of Manitoba. The remaining authors have no conflicts of interest to declare.

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Abbreviations

AE: adverse effect
ALA: alpha-lipoic acid
AST/ALT: aspartate transaminase and alanine transaminase
CONSORT: Consolidated Standards for Reporting Trials
MTD: maximal tolerated dose
NNT: number-needed-to-treat
NP: neuropathic pain
NSAID: nonsteroidal anti-inflammatory drug
PGB: pregabalin
RCT: randomized controlled trial
SF-36: Short Form survey

Edited by G Eysenbach; submitted 10.02.17; peer-reviewed by S Haroutiunian; comments to author 14.04.17; revised version received 21.04.17; accepted 24.04.17; published 08.06.17.

Please cite as:
Gilron I, Tu D, Holden R, Jackson AC, Ghasemlou N, Duggan S, Vandenkerkhof E, Milev R
Pain Improvement With Novel Combination Analgesic Regimens (PAIN-CARE): Randomized Controlled Trial Protocol
JMIR Res Protoc 2017;6(6):e111
URL: http://www.researchprotocols.org/2017/6/e111/
doi:10.2196/resprot.7493
PMID:28596150

Protocol

Somatosensory Modulation of Salivary Gene Expression and Oral Feeding in Preterm Infants: Randomized Controlled Trial

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Abstract

Background: Despite numerous medical advances in the care of at-risk preterm neonates, oral feeding still represents one of the first and most advanced neurological challenges facing this delicate population. Objective, quantitative, and noninvasive assessment tools, as well as neurotherapeutic strategies, are greatly needed in order to improve feeding and developmental outcomes. Pulsed pneumatic orocutaneous stimulation has been shown to improve nonnutritive sucking (NNS) skills in preterm infants who exhibit delayed or disordered nipple feeding behaviors. Separately, the study of the salivary transcriptome in neonates has helped identify biomarkers directly linked to successful neonatal oral feeding behavior. The combination of noninvasive treatment strategies and transcriptomic analysis represents an integrative approach to oral feeding in which rapid technological advances and personalized transcriptomics can safely and noninvasively be brought to the bedside to inform medical care decisions and improve care and outcomes.

Objective: The study aimed to conduct a multicenter randomized control trial (RCT) to combine molecular and behavioral methods in an experimental conceptualization approach to map the effects of PULSED somatosensory stimulation on salivary gene expression in the context of the acquisition of oral feeding habits in high-risk human neonates. The aims of this study represent the first attempt to combine noninvasive treatment strategies and transcriptomic assessments of high-risk extremely preterm infants (EPI) to (1) improve oral feeding behavior and skills, (2) further our understanding of the gene ontology of biologically diverse pathways related to oral feeding, (3) use gene expression data to personalize neonatal care and individualize treatment strategies and timing interventions, and (4) improve long-term developmental outcomes.

Methods: A total of 180 extremely preterm infants from three neonatal intensive care units (NICUs) will be randomized to receive either PULSED or SHAM (non-pulsing) orocutaneous intervention simultaneous with tube feedings 3 times per day for 4 weeks, beginning at 30 weeks postconceptional age. Infants will also be assessed 3 times per week for NNS performance, and multiple saliva samples will be obtained each week for transcriptomic analysis, until infants have achieved full oral feeding status. At 18 months corrected age (CA), infants will undergo neurodevelopmental follow-up testing, the results of which will be correlated with feeding outcomes in the neo-and post-natal period and with gene expression data and intervention status.

Results: The ongoing National Institutes of Health funded randomized controlled trial R01HD086088 is actively recruiting participants. The expected completion date of the study is 2021.

Conclusions: Differential salivary gene expression profiles in response to orosensory entrainment intervention are expected to lead to the development of individualized interventions for the diagnosis and management of oral feeding in preterm infants.

Trial Registration: ClinicalTrials.gov NCT02696343; https://clinicaltrials.gov/ct2/show/NCT02696343 (Archived by WebCite at http://www.webcitation.org/6r5NbJ9Ym)

(JMIR Res Protoc 2017;6(6):e113) doi:10.2196/resprot.7712

KEYWORDS

gene expression; preterm infants; brain; mouth; mechanoreceptors

Introduction

The biological complexities of oral feeding have made it the most advanced neurological milestone of the newborn and a predictor of both short- and long-term developmental outcomes in the at-risk premature neonatal population [1,2]. Successful oral feeing requires the integration of the nervous, craniofacial, gastrointestinal, and respiratory systems, as well as maturation of the sensory systems (vision, hearing, somatosensory, gustatory, and olfactory) and hypothalamic feedback loops of satiety and hunger [3-7]. Given the adverse ex utero environment, the achievement of oral feeding competency is a universal challenge across the extremely premature infant (EPI) population (gestational age<28 weeks). While EPIs represent only a small fraction of those born prematurely (<37 weeks' gestational age) [8], they are most at risk for significant morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia) that exacerbate the challenges of learning to feed orally. Due to their compromised respiratory status, EPIs who develop bronchopulmonary dysplasia (BPD) are at greater risk for oral feeding impairments when compared with gestationally-aged (GA) matched infants who do not develop the disease. These infants have been shown to have more difficulty achieving a coordinated suckle-feeding pattern and demonstrate abnormally long periods of deglutition apnea and irregular breathing patterns during feeding [9-14]. These developmental abnormalities place EPIs, specifically those who develop BPD, at increased risk for multiple short- and long-term medical complications. Indeed, more than 40% of children in feeding disorder programs are former preterm infants, strongly linking long-term feeding difficulties to failed oral feeding trials in the NICU [15]. In addition, premature infants who correct to term post-conceptional age (PCA) and who cannot successfully orally feed have been shown to be at increased risk for developmental disabilities [16,17] and may require surgical insertion of a gastrostomy tube to provide adequate enteral nutrition [18].

There is currently no objective and quantitative tool to assess oral feeding maturity in premature infants. The current standard of care to determine oral feeding readiness in the EPI population is to use largely subjective, qualitative, and unvalidated cue-based assessment tools [19-22]. Caregivers can only rely on their clinical acumen and overall physical and developmental assessments to determine when an infant may safely and effectively feed orally. The majority of neonatal intensive care units (NICUs) use assessment tools that allow EPIs who correct to ≥33 weeks' PCA and who demonstrate appropriate cues with a stable respiratory status to attempt oral feeding trials. These trial-and-error approaches provide no insight into why an infant should fail to orally feed and be unable to assess orocutaneous, neurological, or gastrointestinal developmental stages, particularly at a molecular level. A recent Cochrane Review assessing the benefits of these available feeding assessment tools in reducing hospital length of stay, as well as shortening time to full oral feeds, concluded that "there is no evidence to inform clinical practice" [23]. The review further stated, "research is needed in this area to establish an evidence base for the clinical utility of instruments to assess feeding readiness in the preterm infant population." The lack of an objective assay to accurately assess feeding skills and behavior in this vulnerable population has not only contributed to neonatal morbidities, such as choking, aspiration, and feeding aversions, but has also resulted in prolonged hospitalizations with average medical costs estimated at US $3,500/day [24,25]. Thus, there is a strong need to advance the field through the integration of novel treatment strategies and objective assessment tools to improve oral feeding skills, while identifying aberrant or delayed maturation of specific developmental systems, which limits feeding success.

A new translational application, approved by the FDA in 2008, has been shown to promote ororhythmic motor patterning (nonnutritive suck) in preterm infants who exhibit delayed or disordered nipple feeding behaviors. This approach is based on mechanosensory entrainment of the suck central pattern generator using servo-controlled pulsed pneumatic stimuli to drive peri- and intra-oral afferents, which in turn modulate local reflex activity and produce nonnutritive suck rhythms [26-31]. Since 2008, this innovative device, known as the NTrainer System, has been improving oral feeding skills in the at-risk premature newborn. However, limited data exist that inform caregivers when to initiate the intervention or identify which infants will positively respond.

To address this need, the current study employs neonatal salivary transcriptomics, a rapidly evolving field that utilizes a safe, easily obtained biofluid for health and systemic disease surveillance. Saliva is a diverse source of genetic material, proteins, metabolites, and microorganisms. Through both extracellular and intracellular trafficking mechanisms in the salivary glands, biomarkers enter into the oral cavity and may be monitored to inform an investigator about an infant's development, physiology, and pathophysiology [32,33]. In the past decade, it has been found that an enormous amount of

neonatal developmental gene expression data is available from as little as 10 μ L of saliva [34]. This research has led to the identification of salivary biomarkers that are directly linked to successful neonatal oral feeding behavior [4,35]. However, expression of these genes has only been assessed at two feeding time points: unsuccessful and successful oral feeding. No data currently exist that describe each gene's expression ontology leading up to oral feeding trials or during the process of oral feeding. Thus, this study aims at generating new and critical gene expression data regarding the developmental milestones required for oral feeding competency in this at-risk population. We hypothesize that some or all of these genes will be positively affected by the PULSED NTrainer intervention and alter their gene expression ontology to expedite oral feeding success. Further, gene expression data may accurately identify those infants who will most benefit from the intervention. Gaining access to this developmental information through noninvasive salivary gland gene expression analyses may allow caregivers to make informed and objective decisions about treatment strategies and optimize timing for the initiation of oral feeding trials.

There is extensive evidence from animal models that support the notion that somatosensory experience delivered to trigeminal mechanosensitive afferents and orofacial motor activity causes (1) structural changes in brain circuitry and (2) modulations in gene expression. The orofacial primary somatosensory cortex (S1) is exquisitely responsive to tactile manipulations of the sensory periphery, making it a classic system for studying plasticity in the developing brain in rodents [36-44] and primates [45]. In rodents, the principal sensory nucleus of the trigeminal nerve (PrV) is primarily responsible for transferring whisker-specific topographical patterning to the contralateral ventroposteromedial nucleus of the thalamus (VPm) [46]. Topographical pattern formation follows a sequential order from Orofacial PrV VPm S1 neocortex in the neonatal period [47]. Early patterning of thalamocortical afferents is dependent on the sensory periphery [39]. Removal of a row of whiskers in the neonatal period results in shrinkage of the layer 4 (L4) cortical areas known as "barrels" assigned to each clipped or extirpated whisker, while adjacent barrels mapped to intact whiskers in S1 expand [48]. This effect is far more robust in the neonatal period than at later ages. Maladaptive stimulation or periods of somatosensory deprivation in the neonatal period affect orofacial map formation in PrV, VPm, and S1 [49,50]. Repetitive somatosensory stimulation or changes in the frequency and strength of activation across synapses can cause physiological changes including long-term potentiation (LTP) or long-term depression (LTD) of neurotransmission [51,52]. These data strongly suggest that there are critical periods during which the presence of specific external or internal conditions is necessary for normal development and that the absence of such conditions leads to irreversible alterations in the organism [53]. To further delineate these critical developmental windows, researchers have begun to focus on identifying differential gene expression before, during, and at the closure of the critical period of plasticity at various levels of the trigeminal pathway [39]. Importantly, recent studies have shown that short- and long-term somatosensory stimulation by enriched environment up-regulates cortical expression of neuropeptide messenger RNAs (mRNA) and down-regulates immediate-early gene mRNAs in the rodent S1 barrel cortex, and they suggest a central role of neuropeptides in tuning S1 circuits by somatosensory experience [54,55]. These gene expression data lay the foundation for this study to integrate somatosensory stimulation and gene expression analysis to improve oral feeding in the human neonate.

An obvious extension of this research will be to assess the potential long-term impact of PULSED NTrainer in the neonatal period on the feeding behavior, growth, and neurodevelopmental outcomes of EPIs at 18 months' PCA. It is well established that feeding issues may continue long after an EPI is discharged from the hospital and that resultant poor growth and nutrition negatively impacts neurodevelopment [16,17]. Combined with the existing animal data that strongly suggests that there are critical developmental windows for appropriate somatosensory stimulation, we hypothesize that infants exposed to PULSED NTrainer in the neonatal period will have improved growth and neurological outcomes in the first years of life and that gene expression data will be able to specify such "critical periods."

The purpose of this study is to combine molecular and behavioral methods in an experimental conceptualization approach to map the effects of trigeminal (PULSED orocutaneous) somatosensory stimulation on salivary gene expression in the context of the acquisition of an exquisitely complex oromotor skill, namely oral feeding, in high-risk human neonates. The aims of this study represent the first attempt to combine noninvasive treatment strategies and transcriptomic assessments of high-risk EPIs to (1) improve oral feeding behavior and skills, (2) further our understanding of the gene ontology of biologically diverse pathways related to oral feeding, (3) use gene expression data to personalize neonatal care and individualize treatment strategies and timing interventions, and (4) improve long-term developmental outcomes. This integrative approach to oral feeding is a paradigm shift in neonatal care, where rapidly emerging technological advances and personalized transcriptomics can safely and noninvasively be brought to the neonatal bedside to inform medical care decisions and improve care and outcomes .

Methods

Participants

Only EPIs born between 24 0/7 and 28 6/7 weeks' gestation, as determined by obstetric ultrasound at <15 weeks or last menstrual period, are eligible to participate in this study. We will actively enroll EPIs once they have a corrected PCA of ≥29 weeks to limit the number of infants who develop serious sequelae of prematurity and would not be eligible for this study based upon the criteria listed below. Parents of enrolled subjects will receive a Babies R Us $50 gift card for their participation. Subjects will be recruited from three neonatal intensive care units including (1) CHI Health St. Elizabeth (Lincoln, Nebraska), (2) Tufts Medical Center NICU (Boston, Massachusetts), and (3) Santa Clara Valley Medical Center (San Jose, California) by a study site principal investigator (PI) or co-Investigator or the neonatal study coordinator. Informed consent will be obtained before participants' entry into the study, following consultation with the attending physician and nurse(s).

A total of 180 EPIs (approximately equal numbers of males and females, no exclusion based on race or ethnicity) will participate in the study (power >.85, Type I error <.05).

Exclusion Criteria

EPIs will not be recruited for this study if they have any of the following: (1) chromosomal and congenital anomalies including craniofacial malformation, nervous system anomalies, cyanotic congenital heart disease, gastroschisis, omphalocele, diaphragmatic hernia and other major gastrointestinal anomalies; (2) congenital infection; (3) no documented GA; (4) severe intrauterine growth restriction (IUGR) (3%); (5) abnormal neurological status including head circumference <10th or >90th percentile, intracranial hemorrhage grades III and IV, seizures, meningitis, neurological examination showing abnormal tone or movements of all extremities for PCA; (6) history of necrotizing enterocolitis (stage II and III); and (7) culture-positive sepsis at the time of study enrollment.

Protocol

EPIs will be stratified among two gestational age groups (24 0/7-26 6/7 weeks and 27 0/7-28 6/7 weeks). Each infant will be randomized to receive either the PULSED NTrainer or SHAM intervention using a software random integer function in Minitab version 17. As shown in Figure 1, infants assigned to the PULSED NTrainer group will receive a progressive dose of the pulsatile orocutaneous stimulation. Beginning at 30 weeks' PCA, these infants will receive 2 weeks of low-dose PULSED NTrainer stimulation (2 x 3-minute blocks) with a 1-minute stimulus "off-period" between the stimulation blocks. This form of stimulation will be given simultaneously with tube feedings 3 times/day. The stimulus dose will then be increased over the next 2 weeks (3 x 3-minute blocks of PULSED NTrainer stimulation) with a 1-minute stimulus "off-period" between the stimulation blocks, also given simultaneously with tube feedings 3 times/day. EPIs randomized to the SHAM condition will be given a regular silicone pacifier during tube feedings over the same time period, and will be handled in exactly the same way as those infants in the experimental group of the study, with the exception of the PULSED inputs from the pacifier. To ensure blinding, only study site PIs or co-Investigators and the neonatal study coordinators will be informed of infants' group assignments. Physicians, nurses, and other NICU care staff will not be informed about the infants assigned to the intervention group.

Orocutaneous Stimulation Regimen

The NTrainer PULSED orocutaneous stimulus consists of a series of 6-cycle bursts that are delivered by a servo-controlled pneumatic amplifier (NTrainer System) to the lumen of a standard silicone pacifier (eg, WeeSoothie or Soothie). These pneumatic bursts are frequency modulated (FM) from 2.8 to 1.6 Hz across the 6-cycle structure, with a 2-second pause period between bursts (Figure 2). Individual pressure cycles have a 31 millisecond (ms) rise or fall time to ensure salient stimulus spectra with significant energy from DC-16 Hz [56]. Frequency modulation is a physiologic feature of the nonnutritive suck (NNS) in preterm infants [57]. A total of 34 bursts are presented in a 3-minute block. A 1-minute rest period (no stimulation) occurs between stimulation blocks. Criteria for initiation of orocutaneous therapy include the following: (1) stable vital signs and not on continuous vasopressor medications, (2) tolerating enteral feeds in previous 48 hours, and (3) not intubated and mechanically ventilated. If the infant is on nasal intermittent positive pressure ventilation, continuous positive airway pressure or nasal cannula >2 liters per minute, then the fraction of inspired oxygen (FiO2) must be <40%.

Figure 1. Somatosensory intervention plan for stratified populations of Extremely Premature Infants along with the salivary sampling protocol and digitized measurements of nonnutritive suck progression is shown below, with primary (salivary gene expression, time to attain oral feeds, and nonnutritive suck pattern formation) and secondary (National Institute of Child Human Development Neonatal Research Network feeding-growth questionnaire and Bayley III screener at the neonatal intensive care unit follow-up) outcome variables listed as well.

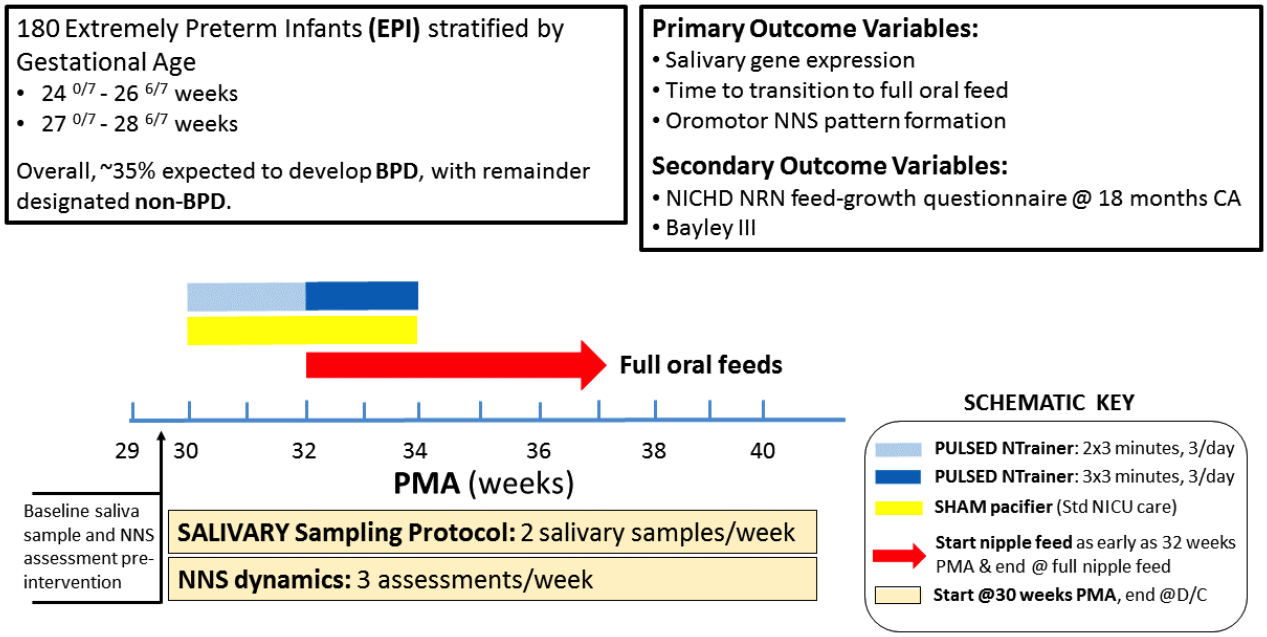
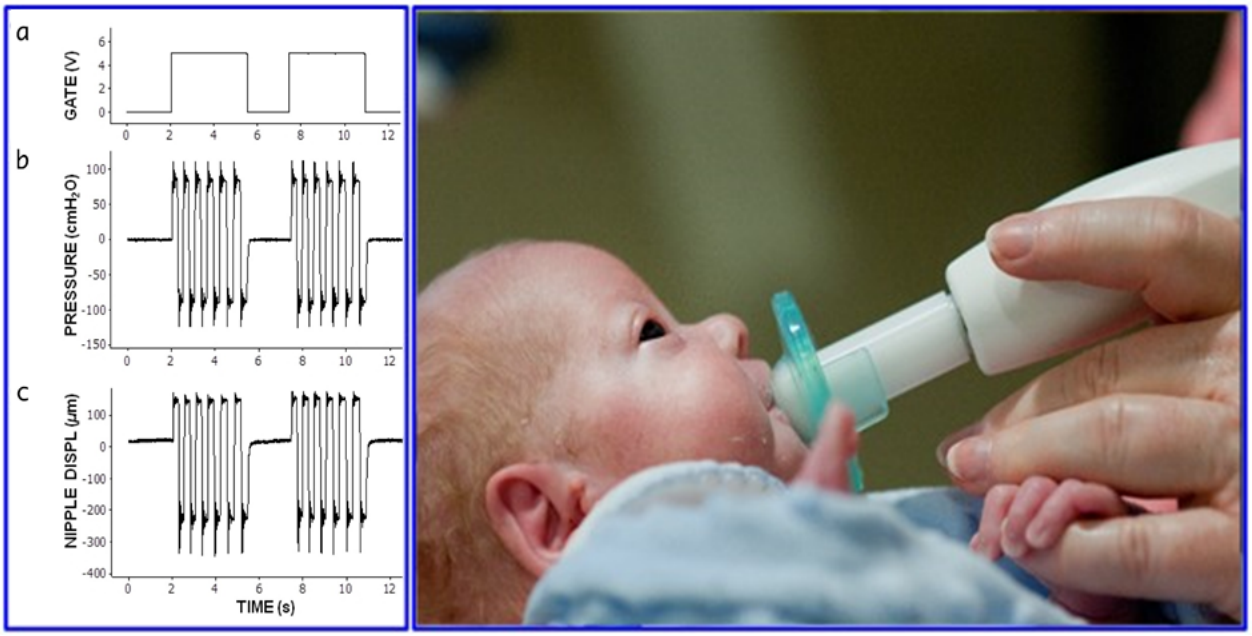


Figure 2. Preterm infant receiving PULSED NTrainer stimulation during gavage feeding in the neonatal intensive care unit, with a nasogastric tube placed through the left nares (not visible); pneumatic stimulus control signals and output through the pacifier nipple are shown in the left panel: (a) voltage-controller gate signal, (b) intraluminal pressure (inside) the nipple, and (c) mechanical displacement at the nipple cylinder wall (Photo courtesy of Innara Health, Inc., Olathe, Kansas USA).



Nonnutritive Suck Assessment and Automated Nonnutritive Suck Digital Signal Processing and Feature Extraction

In addition to the oral stimulation interventions (PULSED NTrainer vs SHAM pacifier), all study infants will be assessed 3 times/week (eg, Monday/Wednesday/Friday) for NNS performance. The NTrainer System will be used in " *assessment mode* " to record the compression dynamics of NNS during a 3-minute session to immediately precede a tube feeding that is not associated with an intervention condition.

The most active 2-minute period of NNS behavior based on suck cycle count is automatically extracted from each suck assessment data file using an automated waveform feature extraction algorithm on the NTrainer System. The NNS pressure waveform is band-pass filtered (0.5-20 Hz) to remove low frequency offsets due to tongue or jaw posturing and thermal drift associated with oral contact on the pacifier bulb and to remove high-frequency jitter. Pressure peaks >1.6 cm H_2O are subjected to feature extraction criteria, including suck cycle symmetry, cycle duration, and burst identification defined as two or more NNS events occurring within 1200 ms. This algorithm permits objective identification of NNS burst activity distinct from non-NNS mouthing compressions or tongue thrusts against the pacifier. Four measures will be objectively extracted from the indexed records of suck compression, including minute-rates for (1) NNS bursts where an individual burst includes 2 or more suck cycles, (2) NNS cycle events defined as suck compression cycles with cycle periods less than 1200 ms, (3) Total oral compressions defined as the sum of all pressure events, and (4) NNS compression pressure expressed in cm H_2O [56-63].

Per os (PO) Feeding Advancement

EPIs will advance on a standardized cue-based feeding schedule utilized by each site NICU, known as Infant Driven Feeding [64,65] that will lead to full nipple feeds. This standardization of oral feeding advancements across sites will limit confounders that may ultimately skew the data.

EPI participant data will be managed with our Neonatal Oromotor Database, custom software developed in the Barlow laboratory specifically for NTrainer studies in the NICU. This database software is compatible with MS WIN 7 8.2, and 10 operating systems and is password-protected and coded as executable for MS ACCESS 2013. This software provides a paperless, efficient system for NICU study personnel to log daily information including GA, growth parameters, medications, oxygen requirement, feeding history, medical procedure log, comments, as well as NTrainer or SHAM and salivary sampling dates on enrolled infants.

Saliva Collection, Processing, and Gene Expression Analysis

Saliva Collection

Saliva samples will be collected from all enrolled infants on the first day, before receiving either the SHAM or PULSED NTrainer intervention. This sample will serve as our baseline gene expression profile. Samples will then be obtained twice per week (~ 3 day intervals) up to the time of achievement of full oral feeds or discharge from the hospital with either a nasogastric tube or gastronomy tube.

Saliva samples at each site will be collected with techniques that have been optimized and validated through the Maron laboratory [66]. Briefly, saliva samples will be collected with a 1 mL syringe, end caps removed and attached to low wall

suction. Saliva will be collected for approximately 20 seconds and immediately stabilized in 500 µL of Qiagen's RNA Protect Saliva to halt gene expression changes, inhibit destructive ribonucleases (RNases), and limit microbial overgrowth. Samples will be vortexed briefly and frozen at −20°C. Once frozen, samples are stable for up to 18 months before the need for total ribonucleic acid (RNA) extraction. Thus, samples from Nebraska and Santa Clara will be shipped once a month on ice overnight to the Maron laboratory at the Mother Infant Research Institute at Tufts Medical Center in Boston, Massachusetts, for processing.

Generation of a Saliva Biobank

One additional saliva sample will be obtained each week from all enrolled subjects to generate a biobank repository. The rationale for this approach is twofold. First, it is possible that during shipment or processing, salivary RNA may be destroyed and not be of sufficient quality to incorporate into the study. Prior studies from this lab have demonstrated a 10% failure rate of gene amplification in saliva samples [4]. Banking an additional sample each week from study subjects will ensure that we will limit loss of data points. Second, we anticipate that there are informative salivary biomarkers of oral feeding maturation that have yet to be identified. By generating a biobank of additional saliva samples that may be retrospectively interrogated on either a microarray gene expression platform or with RNA sequencing, we will have the potential to discover novel hypotheses about gene-gene interactions and/or transcriptional regulatory processes related to oral feeding in the EPI population.

Total Ribonucleic Acid Extraction

Salivary samples will extracted for total RNA using established protocols optimized in the Maron laboratory [66]. RNA extraction will occur with the QIAGEN RNAProtect Saliva Mini kit, per manufacturer's instructions. On column DNase treatment will be performed for each sample to eliminate genomic DNA contamination. Samples that are part of the biobank will be frozen at −80° C, pending need for future analysis. Samples that will be used for quantitative reverse transcription polymerase chain reaction (RT-qPCR) experiments will first undergo complementary deoxyribonucleic acid (cDNA) conversion with the Life Technologies SuperScript Vilo kit, per manufacturer's instructions. cDNA will be stored at −80°C in the Mother Infant Research Institute at Tufts Medical Center, pending gene expression analysis.

Gene Expression Analysis

For the purpose of this study, we will interrogate each sample for nine genes, six target genes of interest and three reference genes for quality control and potential normalization of gene expression data. Genes to be analyzed in this study have been previously shown to be directly linked to oral feeding in the newborn and include *PLXNA1*, *PLXNA3*, *NPY2R*, *WNT3*, *AMPK*, and *NPHP4*. The three reference genes include *GAPDH*, *HPRT1*, and *YWHAZ*, all of which have been shown to maintain stable gene expression across advancing PCA [67]. All cDNA samples will undergo targeted preamplification with a custom TaqMan PreAmp Master Mix for all nine genes. This targeted approach to amplification will ensure that only those genes of interest will be amplified and not all genes across the transcriptome that may introduce bias. Preamplified cDNA will then undergo PCR with TaqMan Fast Advance Master Mix on the Life Technologies Quant Studio 7 Flex Real-Time PCR System. This instrument is housed at the Mother Infant Research Institute at Tufts Medical Center and is an advanced state-of-the-art polymerase chain reaction (PCR) machine and software system. All efforts will be made to adhere to the Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guidelines for this study [68]. All samples will be run in duplicate with appropriate positive and negative controls.

Initial Gene Expression Analyses

All gene expression data will be normalized on the Quant Studio 7 Flex Real-Time PCR System. Only samples that have successful amplification of all three reference genes will be considered in the analysis. Previously, genes have been informative in a binary fashion (+/- expression) [4]. However, for the purpose of this study, we will be prepared to calculate relative gene expression of each target gene with the delta delta cycle threshold (ΔΔCt) method [69]. In accordance to the MIQE guidelines, we will use the three reference genes for normalization and determine a geometric mean of their Ct in each sample to calculate relative gene expression [66]. Normalized data will then be given to our statistician and bioinformatic collaborator for analysis.

Neurodevelopmental Follow-Up

Each center site in this study has a Neonatal Follow-Up Clinic that performs neurodevelopment testing on EPIs from discharge up to three years of life by certified examiners as part of standard of care. Thus, developmental follow-up data will be available from all study subjects, regardless of intervention and free of charge. As part of standard of care, each site will complete the Bayley Scales of Infant and Toddler Development 3rd Edition [70] on EPIs at 18 to 24 months' corrected age. The primary subtests of interest include *Fine Motor* (prehension, motor speed and planning, perceptual-motor integration, reaching, grasping, and object manipulation), *Gross Motor* (dynamic movement, including walking, jumping, running, stairs, and so on; motor planning; balance; and perceptual-motor integration), *Cognition* (puzzle assembly, object completion, means-ends manipulation, representational play, counting, and matching colors), and *Language* (receptive and expressive language). These data will be recorded, analyzed, and correlated with feeding outcomes in the neo-and post-natal period and with gene expression data and intervention status. In addition, growth parameters including head circumference, length, and weight will be recorded.

Feeding behavior plays a significant role in neurodevelopmental outcomes. Recent findings from the NICHD Neonatal Research Network (NRN) indicated that at 18 months' CA, premature infants with a history of feeding difficulties are more likely to have language delay. Neuromotor status and days on mechanical ventilation are important risk factors associated with these outcomes [71]. A follow-up of feeding status will be completed when our study infants reach 18 months' CA, using the NICHD NRN 18-month Feeding-Growth-Nutrition Questionnaire. This

questionnaire includes a simple checklist format about medical history since the NICU (re-hospitalization, primary cause, time period, LOS, and time in ICU), medications, seizures, supplemental oxygen and respiratory monitoring, oromotor skills (independent feeds, dependent oral feeds, limited oral feeding, and no oral feeding), nasogastric (NG) or total parenteral nutrition (TPN) feeds, feeding behaviors (aversion and swallowing-dysphagia), aspiration (food down windpipe or choking), spit-ups, high calorie supplements, oral diet texture (thin vs thickened liquids, soft solids, and table food), and surgical operations. Completion time by the parent is 15 minutes or less. The feeding questionnaire and a pre-posted return envelope will be mailed to the parent when a given study infant attains 17.5 months of age. A cover letter will accompany the 3-page questionnaire explaining that a nurse or study specialist from this research project will be available to assist with the questionnaire.

Statistical Analysis

To address the relationship between PULSED NTrainer stimulation and salivary gene expression profiles and duration to full oral feeds, descriptive statistics and bivariate tests will examine the associations of gene expressions with successful oral feeding at each measurement time point. Diagnostic performance statistics, such as sensitivity, specificity, positive predictive value, and negative predictive value, will also be computed for each selected gene. Frailty modeling techniques will compare the time to full oral feed between SHAM and PULSED NTrainer treatments. Given the clustered longitudinal structure of our data (ie, EPIs at three NICUs are observed repeatedly over a 6- to 8-week period), a mixed modeling approach will be used to properly account for dependency among observations. Specifically, general or generalized mixed models will estimate overall group difference between SHAM and PULSED NTrainer treatments (group effect), developmental pattern over time (time effect), and group difference in this pattern (time-by-group interaction) separately for gene expressions, NNS formation, and oral feeding skills. A significant group effect and/or time-by-group interaction will indicate significant intervention effect. Models will include GA, PCA, sex, and antenatal steroids as covariates, thereby providing unbiased estimates of intervention effects. In subsequent mixed modeling of feeding status as a dependent variable, we will calculate the odds ratio (OR) and 95% CI for successful oral feeding in association with the expression of each gene. Grids of estimated probabilities of full oral feeding for different combinations of gene expressions, NTrainer treatments, GA, PCA, and sex will be constructed. In secondary analyses, the proposed statistical analyses will be conducted separately among BPD and non-BPD EPIs. All analyses will be conducted using R and SAS 9.4 [72].

To address the power and accuracy of predicting oral feeding status with the use of feeding-readiness gene expression profiles and NTrainer treatments, generalized linear models with a logit link (ie, logistic regression) will be evaluated separately for different infant subgroups of GA, PCA, sex, and BPD status. For example, the coefficient of determination (R^2) and area under the curve (AUC) estimated at each measurement time point will suggest the presence and timing of critical periods when oral somatosensory stimulation may enhance or inhibit oral feeding attainment. Also, learned Bayesian networks will be applied to the gene expression data to identify informative gene clusters that discriminate between neonates who received PULSED NTrainer and those who received SHAM. We will further differentiate subjects for whom PULSED NTrainer was an effective intervention to improve feeding outcomes and for those in whom it was not [73]. Data analysis will be performed in a three stage sequence including data preparation, selection of predictive gene clusters, and Bayesian network probabilistic analysis. Data will first be organized into two datasets: one that includes all gene expression data and one that includes gene expression data from the last sample obtained (LSO) at the end of the intervention. Six datasets will then be generated: (1) all screening observations; (2) all data from LSO; (3) differenced observations from SHAM, responders, and nonresponders; (4) differenced nonresponders and SHAM; (5) differenced nonresponders and responders; and (6) differenced responders and SHAM. The “all screening observation” dataset will be used as a baseline measure for the other five partitions in the predictive models.

Bayesian network structure and parameter estimates will be learned directly from study generated data partitions listed above (1-6) [74]. The program will assume an equal likelihood for all models, sequentially searching the set of all models and then assigning a network score based on either Bayes Factor (BF) or Akaike Information Criterion (AIC) criteria. A heuristic search algorithm (K2 algorithm) will be used to traverse the model space [75]. As both gene expression levels (absolute or binary [+/- gene expression]) and changes in gene expression (differenced) may be predictive of response to the PULSED NTrainer intervention, we will consider both in our analysis. To identify which gene ontological profiles were critical to the predictive value of the Bayesian network models, the gene clusters found in the baseline screening data will be mapped on the LSO Bayesian network using the BF score type. We will examine the importance of these genes’ expression ontology profiles in defining responders and nonresponders by re-evaluating network prediction accuracy.

In order to mathematically model both the transition time-to-oral feeds and salivary gene expression profiles with their predictive relationships to infant feeding, growth, and neurodevelopmental outcomes at 18 months’ CA, general mixed models (ie, individual growth models) will be used to identify the developmental pattern of change (time effect) in NNS formation, salivary gene expression profiles, and oral feeding skills. The change pattern will be compared between SHAM and PULSED NTrainer treatments, BPD conditions, and their combinations as interactions with the time effect in the models. Then, these data will be combined with the NICHD NRN feed-growth-nutrition data and Bayley III (raw and standardized) scores of cognitive, motor, and language skills at 18 months’ CA. General linear models (ie, regression) will examine the predictive power of oral feeding and NNS oromotor skills at the exit of the NICU on the feeding, growth, and Bayley III subtest markers at 18 months’ CA. In separate models, these outcomes will be compared between SHAM and PULSED

NTrainer treatments (ie, multivariate analysis of covariance). All models will include GA and sex as covariates.

Sample Size and Power

This study will utilize a stratified random sampling method, where 180 EPIs stratified by GA (24 0/7-26 6/7 weeks or 27 0/7-28 6/7 weeks) are randomly assigned to SHAM or PULSED NTrainer treatment within each GA stratum. Of the 180 EPIs, we expect 35.0% (63/180) will develop BPD. This estimate is based on an evaluation of the incidence of BPD among EPIs at the 3 participating NICUs. The total sample size of 180 has been determined in order to achieve adequate statistical power in evaluating the effectiveness of NTrainer stimulation. With regard to the analyses on gene expression profiles, we estimated effect sizes corresponding to the treatment group differences in diagnosis accuracy for the most predictive genes of feeding success. Anticipating that SHAM infants will show sensitivity and specificity levels comparable to the values observed in Maron et al [4] and that PULSED infants will provide greater levels of sensitivity and specificity (an increase by 0.10; ie, enhanced expression of those genes), the estimated effect sizes are in the small to medium range (Cohen *f*=0.10-0.19; see Table 1). Given these estimates, a sample of 180 infants is expected to provide, on average, 82-85% power (range=78-96%) to compare the predictive associations of gene expressions with oral feeding status, even under a high attrition rate of 20%.

Our recent NTrainer trial (NIH DC003311) with preterm infants [56,59] also indicated moderate effects on the primary NNS oromotor measures (*f*=0.22-0.26; see Table 2). Power analysis based on this empirical data reveals that the analyses on NNS formation and oral feeding skills will have, on average, 96% power (range=95-98%), with the sample size of 180 and 20% attrition rate. We will error on the conservative side of our power calculation and, therefore, recruit a total of 180 infants, which is expected to yield 63 BPD and 117 non-BPD EPIs. After 20% attrition, the net number of EPIs is 50 BPD and 94 non-BPD.

Table 1. Effect size and power for genetics measures.

Gene	Sensitivity[a]	*f*	Power	Specificity[a]	*f*	Power
PLXNA1	0.85	0.17	0.93	0.23	0.11	0.81
AMPK	0.96	0.19	0.96	0.08	0.15	0.90
WNT3	0.17	0.12	0.83	0.72	0.12	0.83
NPY2R	0.39	0.10	0.78	0.53	0.10	0.78
NPHP4	0.58	0.10	0.78	0.35	0.10	0.78
Average		0.14	0.85		0.12	0.82

[a]values from Maron et al [4].

Table 2. Effect size and power for nonnutritive suck oromotor measures.

Variable	SHAM[a], mean (SD)	PULSED[a], mean (SD)	*f*	Power
NNS[b] Bursts/minute	7.85 (2.36)	8.79 (1.93)	0.22	0.95
NNS[b] events/minute	64.67 (22.18)	74.92 (20.37)	0.24	0.96
Total oral compressions/minute	71.02 (24.66)	83.75 (23.67)	0.26	0.98
Average			0.24	0.96

[a]Values from Barlow et al.

[b]NNS: Nonnutritive suck.

Results

This ongoing National Institutes of Health (NIH) funded research is being conducted at three NICUs across the United States: (1) CHI Health St. Elizabeth (Lincoln, Nebraska), 2) Tufts Medical Center (Boston, Massachusetts)], and (3) Santa Clara Valley Medical Center (San Jose, California). The research protocol has been approved by each site's Institutional Review Board (IRB). Participant recruitment began in July 2016, and NTrainer intervention is expected to be completed by 2020. Neurodevelopmental follow-up testing will begin in 2018.

The primary outcome variables include salivary gene expression of a panel of genes previously identified as playing a role in oral feeding of preterm infants, time to transition to full oral feeding, and oromotor NNS pattern formation. Secondary outcome variables include: NICHD NRN 18-month Feeding-Growth-Nutrition Questionnaire, and Bayley III scores of cognitive, motor, and language skills at 18 months' corrected age (CA).

Discussion

Oral feeding is a complex neurological milestone that can pose a significant challenge for many preterm infants, particularly for those born extremely prematurely (<28 weeks gestational age), as well as those with a compromised respiratory status. Persistent feeding difficulties can result in numerous short- and

long-term medical complications, as well as place infants at risk for developmental disabilities. Currently, there is no objective method for treating delayed or disordered feeding skills, or for assessing oral feeding maturity. Therefore, there is a strong need for objective assessment tools and novel therapeutic interventions to identify the underlying mechanisms that delay and disrupt oral feeding success and provide evidence-based intervention strategies to help ameliorate outcomes. The current study aims to combine safe, noninvasive treatment strategies and salivary diagnostics in EPIs to improve oral feeding skills as well as long-term neurodevelopmental outcomes and to further our understanding of the gene ontology of biological pathways related to oral feeding, which may ultimately individualize the type and timing of interventions and personalize neonatal care.

Acknowledgments

This research is funded by the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD) (R01 HD086088).

Authors' Contributions

SMB, JLM, DS, PJ, and BG were responsible for the conception and experimental design of this NIH RCT, as well as for fiscal management, project execution and coordination among NICUs, and dissemination of experimental findings. GA was responsible for the computational biomedical cybernetics and modeling of gene expression data sampled from extremely preterm infants among the three participating NICU and dissemination of experimental findings. BJW shared responsibility for the conception and experimental design of this NIH RCT, project execution at the CHI Health St. Elizabeth's NICU, and dissemination of experimental findings. JL shared responsibility for the computational biostatistics and modeling of neurodevelopmental outcomes and biomechanical measures of suck ororhythmic activity, which informed the experimental design of this NIH RCT for data collected at all three NICUs, and dissemination of experimental findings. AOR was the study coordinator at Tufts Medical Center NICU, and under the direction of Dr Maron, conducted RNA processing and handling for salivary samples collected at each NICU site.

Conflicts of Interest

None declared.

Multimedia Appendix 1

NIH summary statement - study section peer review.

[PDF File (Adobe PDF File), 129KB - resprot_v6i6e113_app1.PDF]

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Abbreviations

BPD: bronchopulmonary dysplasia
CA: corrected age
cDNA: complementary deoxyribonucleic acid
EPI: extremely preterm infant
FiO2: fraction of inspired oxygen
IUGR: intrauterine growth restriction
mRNA: messenger RNA
National Institute of Child Human Development: NICHD
National Institutes of Health: NIH
NG: nasogastric
NNS: nonnutritive suck
NRN: neonatal research network
PCR: polymerase chain reaction
PI: principal investigator
PMA: postmenstrual age
PO: per os
RNA: ribonucleic acid
RNase: ribonuclease
RT-qPCR: quantitative reverse transcription polymerase chain reaction
TPN: total parenteral nutrition

Edited by G Eysenbach; submitted 20.03.17; peer-reviewed by C Lau, B Singh; comments to author 12.04.17; accepted 28.04.17; published 14.06.17.

Please cite as:
Barlow SM, Maron JL, Alterovitz G, Song D, Wilson BJ, Jegatheesan P, Govindaswami B, Lee J, Rosner AO
Somatosensory Modulation of Salivary Gene Expression and Oral Feeding in Preterm Infants: Randomized Controlled Trial
JMIR Res Protoc 2017;6(6):e113
URL: http://www.researchprotocols.org/2017/6/e113/
doi:10.2196/resprot.7712
PMID:28615158

Protocol

Early Interventions Following the Death of a Parent: Protocol of a Mixed Methods Systematic Review

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Abstract

Background: Previous meta-analyses examined the effectiveness of interventions for bereaved children showing small to moderate effect sizes. However, no mixed methods systematic review was conducted on bereavement interventions following the loss of a parent focusing on the time since death in regard to the prevention of grief complications.

Objective: The overall purpose of the review is to provide a rigorous synthesis of early intervention after parental death in childhood. Specifically, the aims are twofold: (1) to determine the rationales, contents, timeframes, and outcomes of early bereavement care interventions for children and/or their parents and (2) to assess the quality of current early intervention studies.

Methods: Quantitative, qualitative, and mixed methods intervention studies that start intervention with parentally bereaved children (and/or their parents) up to 6 months postloss will be included in the review. The search strategy was based on the Population, Interventions, Comparator, Outcomes, and Study Designs (PICOS) approach, and it was devised together with a university librarian. The literature searches will be carried out in the Medical Literature Analysis and Retrieval System Online (MEDLINE), PsycINFO, Excerpta Medica Database (EMBASE), and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The Mixed Methods Appraisal Tool will be used to appraise the quality of eligible studies. All data will be narratively synthetized following the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews.

Results: The systematic review is ongoing and the data search has started. The review is expected to be completed by the end of 2017. Findings will be submitted to leading journals for publication.

Conclusions: In accordance with the current diagnostic criteria for prolonged grief as well as the users' perspectives literature, this systematic review outlines a possible sensitive period for early intervention following the death of a parent. The hereby presented protocol ensures the groundwork and transparency for the process of conducting the systematic review.

Trial Registration: International Prospective Register of Systematic Reviews (PROSPERO) CRD42017064077; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017064077 (Archived by WebCite at http://www.webcitation.org/6rMq6F0fv)

(JMIR Res Protoc 2017;6(6):e127) doi:10.2196/resprot.7931

KEYWORDS

early intervention; parental loss; protocol; mixed methods; systematic review

Introduction

Background

This paper presents the study protocol of a mixed methods systematic review on early bereavement interventions following the loss of a parent, adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines (PRISMA-P) [1]. This protocol paper seeks to strengthen the quality, reliability, and transparency all the way through the completion of the systematic review.

The death of a parent has been documented as a major stressful and disturbing experience for children [2,3]. Parentally bereaved children are more prone to functional impairment and other multiple negative outcomes, including psychological and behavioral problems [4,5]. Although former clinical assumptions stressed children's lack of ability to grieve [6], it is now well accepted that bereaved children experience a grieving process [7] and some may develop extended psychiatric conditions [8-11]. Moreover, the death of a parent is also associated with an increased mortality risk in children [12,13]. As a result, a diversity of theoretical frameworks and psychosocial interventions have been proposed.

Grief intervention usually consists of quite diverse intervention approaches such as, for example, self-help, family interventions, support groups, counseling, and therapy. Such interventions are delivered by a variety of (para)professionals (eg, psychologists, social workers, nurses, pastoral staff) in varied formats (eg, individual or group, Internet, telephone, home visiting) [14]. Similarly to what was shown in the literature for bereaved adults [15], quantitative reviews on the effectiveness of bereavement interventions for children showed small to moderate effect sizes [16,17]. Nonetheless, interventions targeting high-risk children [16,17] and interventions starting closer to the loss were proved to be more effective [16]. On average, the length of time to initiate intervention after the death was a year and a half, but several studies presented a time interval of 5 years postloss.

An emphasis has been placed in starting interventions early in the mourning process [18,19]. When interventions take place later in the mourning trajectory, children may not be focused on their loss any longer and may have changed in a maladaptive way [16]. Therefore, early psychological interventions for bereaved children and their parents have been highlighted as a tool to decrease acute distress levels [20] and prevent future psychopathology [11,21], namely posttraumatic and complicated grief reactions [22]. In addition, bereaved parents require early qualified help not just for themselves but for their children in particular [23,24]. Likewise, bereaved children ask for early notification and involvement [25,26]. Nevertheless, contradicting results concerning grief therapy for adults still prevail. While some documented that interventions closer in time to the death are more effective [18], others did not find a significant relation between the effect of time since loss on outcome [15]. Additionally, a meta-analysis examining the short- and long-term effects of grief interventions for adults did not support the usefulness of preventive approaches [19]. The authors pointed out a series of methodological limitations among preventive studies such as, for instance, the lack of proper grief measures in screening at-risk groups. However, they did not elaborate on the fact that some studies did not report the mean time since death at study entry, whereas other studies reported a broad time range of 1 month to 2 years postloss. Such diverse timeframes have been noticed as one of the accountable variables for lowering the main effects of grief interventions [16,27].

According to the *International Classification of Diseases*, 11th Revision (ICD-11) and the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5), it looks like the long time intervals of the contemporary quantitative reviews run counter to the viewpoint emphasizing early intervention. The proposal for ICD-11 revision acknowledges grief reactions as a possible form of psychiatric disorder whenever severe grief complications persist beyond 6 months postloss [28]. The current DSM-5 revision suggests a minimal watchful period of 6 months postloss for children and 12 months for adults [29]. A previous review suggested that grief counseling would be more successful if provided within 6 to 18 months following the death. However, this same review also considered that different types of support may be required early and/or later in the bereavement process [27]. Despite the fact that the focus on early intervention has been raised by both clinicians and researchers, there is a profound lack of unanimity. Its conceptualization, timeframes, and effectiveness have not been thoroughly explored. The dearth of high-quality and methodologically equivalent studies [30-32] seem to have led to the general conclusion that the grief field remains in its infancy [33].

Building on the existing quantitative reviews for bereaved children, evidence from qualitative, quantitative, and mixed methods studies will be collected. Based on the ICD-11 and DSM-5 diagnosing systems and the users' perspectives studies, the mixed methods systematic review will focus on intervention studies initiated within 6 months after parental death in regard to the prevention of grief complications. The bereavement interventions will be dependent on the child's age (≤18 years of age), a setting that is compatible with the early intervention standpoint of promoting an optimal developmental trajectory.

Objectives

The overall purpose of the mixed methods systematic review is to provide a rigorous synthesis of early intervention after parental death in childhood. The following two questions will be addressed:

1. What are the rationales, contents, timeframes, and outcomes of early bereavement care interventions for children and/or their parents?
2. What is the quality of current early bereavement care intervention studies for children and/or their parents?

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [34] will guide the completion and reporting of the systematic review. The Covidence online systematic review platform (www.covidence.org) will be used to support the screening, selection, and data extraction stages.

Eligibility Criteria

As shown in Textbox 1, the Population, Interventions, Comparator, Outcomes, and Study Designs (PICOS) structured approach [34] is used to frame inclusion and exclusion criteria for studies. In view of the overall family context, each study will contemplate parentally bereaved children (≤18 years of age) and/or their parents with no limits on further sociodemographic indicators such as gender, ethnicity, or socioeconomic status. Any causes of parental death will be included, whether due to illness, accidents, or other causes. Any type of bereavement psychosocial intervention (eg, crisis intervention, support groups, counseling) starting up to 6 months postloss will be included.

The review will encompass all types of study designs (quantitative, qualitative, and mixed methods). It will include studies published in English language peer-reviewed scientific journals as well as dissertations. Exclusions will apply to systematic or other forms of literature reviews, letters, commentaries/editorials, and conference abstracts/presentations. Study protocols will only be consulted to provide deficient details of later related articles.

Textbox 1. Study eligibility criteria.

PICOS framework:

Population

- Inclusion—parentally bereaved children and/or their parents
- Exclusion—children aged >18 years

Interventions

- Inclusion—any type of bereavement intervention starting within the first 6 months postloss
- Exclusion—any type of bereavement intervention starting after 6 months postloss

Comparator

Not applicable in the context of this mixed methods systematic review

Outcomes

Not applicable in the context of this mixed methods systematic review

Study design(s)

- Inclusion—peer-reviewed quantitative, qualitative, and mixed methods studies and dissertations
- Exclusion—systematic or other forms of literature reviews, stand-alone study protocols, letters, commentaries/editorials, and conference abstracts/presentations

Screening and Selection Process

Two reviewers (MP and IJ) will independently undertake the database searches. An initial-stage screening of titles and abstracts will be performed, and the studies will be assessed against the predetermined inclusion and exclusion criteria. Articles that explicitly do not meet the eligibility criteria will be excluded, while potentially eligible studies will be imported into EndNote citation software (Clarivate Analytics) and duplicates will be deleted. The full text of potentially eligible articles and studies for which a decision grounded on title/abstract cannot be made will be saved for investigation. Any disagreements will be reconciled through discussion and achieving consensus. A second-stage screening of the full-text articles will be independently conducted by MP and IJ for further eligibility assessment. Reasons for exclusion will be documented for future inclusion in the PRISMA flow diagram [34]. Following this, a citation search of all eligible studies and any pertinent reviews attained during the first- and second-stage screenings will be performed to search for additional studies. Once again, disagreements will be resolved via discussion. Multiple articles pertaining to the same study will be gathered and placed under the main study.

Data Sources and Search Strategy

A comprehensive literature search will be carried out on the largest medical, psychological, and nursing databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) (via Ovid), PsycINFO (via Ovid), Excerpta Medica Database (EMBASE) (via Ovid), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) (via EBSCO). To secure a contemporary overview, possible eligible studies will be searched from January 1980.

The search strategy was developed using the PICOS framework [34]. It was informed by the methods sections of previous reviews on bereavement interventions [32,35] and was devised together with a university librarian. The search terms will combine keywords referring to the intervention and the population. Table 1 shows an example of the MEDLINE search strategy that will also be used for the other databases. There will be no methodological filters so that quantitative, qualitative, and mixed methods studies can be screened.

Table 1. MEDLINE search strategy.

Number	Search terms
1	interven*.ti,ab,id.
2	program*.ti,ab,id.
3	counsel*.ti,ab,id.
4	support*.ti,ab,id.
5	prevent*.ti,ab,id.
6	1 or 2 or 3 or 4 or 5
7	exp "Early Intervention (Education)"/ or exp Crisis Intervention/
8	6 or 7
9	death.ti,ab,id.
10	dying.ti,ab,id.
11	grie*.ti,ab,id.
12	los*.ti,ab,id.
13	9 or 10 or 11 or 12
14	parent*.ti,ab,id.
15	father*.ti,ab,id.
16	mother*.ti,ab,id.
17	care-giver*.ti,ab,id.
18	caregiver*.ti,ab,id.
19	14 or 15 or 16 or 17 or 18
20	13 ADJ3 19
21	exp Parental Death/
22	20 or 21
23	8 and 22

Data Extraction

A data extraction template was developed using Cochrane existing guidelines [36] as well as current proposals identifying central aspects of interventions [37]. It comprises information concerning (1) eligibility (eg, child's age, time since death, reasons for exclusion); (2) study characteristics (eg, aims, design, causes of death); (3) participant demographics (eg, age, sex, socioeconomic status); (4) intervention features (eg, theoretical basis, setting, contents/components); and (5) outcomes (eg, frameworks, types of measurements). This data extraction form was independently piloted by two reviewers (MP and IJ).

Despite the likelihood of some unreported data, specifically regarding intervention features, this review will not ask original authors to provide additional information. This is in line with the overall aim to specify and qualify what has been disclosed in peer-reviewed publications. Two reviewers (MP and IJ) will independently extract the data and disagreements will be reconciled through discussion.

Quality Assessment

The interest in mixed methods studies has been increasing over the last 2 decades. However, the emergence of mixed methods systematic reviews is rather novel and there is no consensus regarding its best critical appraisal measures [38]. The Mixed Methods Appraisal Tool (MMAT) [39] consists of a pilot-tested quality assessment instrument that simultaneously assesses the most prevalent types of quantitative, qualitative, and mixed methods studies. The MMAT was chosen because it allows different study designs to be qualified with the same measure. It was specifically developed to be used in mixed methods systematic reviews [38], and it has been used by others in the grief field [35].

Two reviewers (MP and MH) will independently use the MMAT to assess the quality of eligible studies. Both quality scores and general brief descriptions will be provided, and the results will be compared for consistency. Disagreements will be resolved by discussion.

Data Synthesis

Since this review covers a wide range of research designs and multiple findings, it will make use of an interpretative framework. This approach is well suited to systematic reviews including studies expected to be too heterogeneous to ensure a quantitative overview [40]. The Guidance on the Conduct of Narrative Synthesis in Systematic Reviews, proposed by Popay and colleagues [40], will be followed. It seeks to "tell the story"

of the review findings through the iterative implementation of four stages: (1) developing a theory of how the intervention works, why, and for whom; (2) developing a preliminary synthesis of findings of included studies; (3) exploring relationships in the data; and (4) assessing the robustness of the synthesis. In line with these guidelines, a number of different tools and techniques (eg, textual descriptions, tabulation, grouping and clusters, qualitative case descriptions, and reflecting critically on the synthesis) will be used to accommodate the data at each stage. This will be done through an iterative and inductive process, and the emerging results will be discussed with the research team throughout.

Results

This systematic review is in progress. The data search has started and the review is planned to be completed by winter 2017. The results will be submitted to leading journals for publication.

Discussion

The systematic review planned in this protocol paper will convey an up-to-date picture of early intervention after parental death in childhood. The bereavement interventions will be dependent on the child's age (≤18 years of age). This setting is very important to the early intervention field, which seeks to prevent initial dysfunctional manifestations and promote a more adaptive developmental pathway [22]. Although previous meta-analyses were carried out to inspect the effectiveness of interventions for bereaved children [16,17], none has focused exclusively on the loss of a parent or the length of time since death as regard to the prevention of grief complications. The present protocol delimits the timing to start intervention within 6 months postloss, thus it may convey a pertinent boundary for early bereavement care. The rationale for this period is grounded in the current ICD-11 and DSM-5 diagnostic criteria, as well as the literature granting voice to the bereaved families' needs. Another important feature is the inclusion of qualitative, quantitative, and mixed methods designs. Mixed methods reviews, and their reliance on narrative synthesis, broaden the interventions' background and the explanations for their impact, resulting in more thorough implications for future research, policy, and practice [41,42]. Additional strengths are the use of contemporary recommendations for describing interventions [37]. These guidelines were slightly adjusted to the bereavement intervention field and added to our data extraction template. A precise and complete description of the interventions is an essential condition for comparing studies, relating intervention components and outcomes, testing theory [37], and transferring results into clinical practice [43].

While researchers have been calling for more homogeneous and methodologically sound studies [30-32], bereavement care services have developed practices based on experience and feedback from the users of the services. This mixed methods systematic review has the potential to shed light on much of the uncertainty around the conceptualization and helpfulness of preventive bereavement interventions for children who lose a parent to death. It will provide a rigorous synthesis of the rationales, contents, timeframes, and outcomes of early bereavement care interventions following the death of a parent in order to compile evidence about the results and quality of current intervention studies. These findings will convey an important input to recommendations of good practice concerning both research and public mental health care.

Acknowledgments

This work is funded by Statoil and supported by SkatteFUNN (The Norwegian Research Council, project number 252090). The funders have no role in designing and writing this paper, and they will not be involved in the conclusion of the systematic review. We are grateful to Kjersti Aksnes-Hopland, a librarian from University of Bergen, for providing support and guidance during the development of the database search strategy.

Conflicts of Interest

None declared.

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Abbreviations

CINAHL: Cumulative Index to Nursing and Allied Health Literature
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5thEdition
EMBASE: Excerpta Medica Database
ICD-11: International Classification of Diseases, 11thRevision
MEDLINE: Medical Literature Analysis and Retrieval System Online
MMAT: Mixed Methods Appraisal Tool
PICOS: Population, Interventions, Comparator, Outcomes, and Study Designs
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

Edited by G Eysenbach; submitted 27.04.17; peer-reviewed by P Pluye, J Limonero; comments to author 24.05.17; revised version received 06.06.17; accepted 07.06.17; published 29.06.17.

Please cite as:
Pereira M, Johnsen I, Hauken MA, Kristensen P, Dyregrov A
Early Interventions Following the Death of a Parent: Protocol of a Mixed Methods Systematic Review
JMIR Res Protoc 2017;6(6):e127
URL: http://www.researchprotocols.org/2017/6/e127/
doi:10.2196/resprot.7931
PMID:28663165

Proposal

Prevalence of and Risk Factors for Childhood Asthma, Rhinitis, and Eczema in Hong Kong: Proposal for a Cross-Sectional Survey

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Abstract

Background: Previous studies have shown that particulate matter is a major problem in indoor air quality in Hong Kong schools, but little has been done to assess its relationship with health indicators in the children attending those schools. Our study aims to address this research gap by collecting aerosol data in schools to examine the link between different air pollutants with childhood respiratory health. It is important to explore whether or not the prevalence of asthma, allergic rhinoconjunctivitis, and eczema are increasing in local children.

Objective: Our aim is to (1) examine the prevalence of asthma, allergic rhinitis, and eczema in school children aged 6-7 years in Hong Kong between 2001 and 2017, and (2) measure air quality at primary schools and explore its relationship with health outcomes measured by the International Study of Asthma and Allergies in Childhood (ISAAC) survey.

Methods: This is a cross-sectional study consisting of an ISAAC questionnaire and aerosol data collection. We have recruited over 2000 parents of primary school students aged 6-7 years old for the questionnaire, and so far 19 schools have completed aerosol data collection.

Results: The study is expected to be completed this year.

Conclusions: We predict that our study will show a significant change in the prevalence of asthma, allergic rhinitis, and eczema in school children aged 6-7 years old in recent years. In addition, we expect to show a significant association between air quality at school and health outcomes measured by the ISAAC survey.

(JMIR Res Protoc 2017;6(6):e106) doi:10.2196/resprot.7252

KEYWORDS

child health; ISAAC; air pollution; asthma; eczema; rhinitis

Introduction

The prevalence of asthma and allergic diseases has increased substantially in past decades, imposing a significant disease burden on patients, their families, and society [1-5]. Yet recent studies indicate wide global variation in the prevalence of asthma, allergic rhinoconjunctivitis (AR), and eczema, with a growing trend in developing countries and a plateau or even a decreasing trend in developed countries [6]. It has been speculated that environmental and lifestyle factors may continue to induce asthma symptoms in susceptible individuals until the saturation level in prevalence, determined by the genetic composition of the population, is achieved [7]. Local surveys are essential to assess disease burden in terms of prevalence,

economic impact, and effects on quality of life in order to prioritize resource allocation.

The International Study of Asthma and Allergies in Childhood (ISAAC) is the largest worldwide collaborative research project, involving more than 100 countries and nearly 2 million children. It was designed to compare the prevalence of these disorders between populations in different countries, thereby forming the basis for studies investigating the role of possible modifiable environmental factors that may lead to a reduction in the burden of these diseases [8]. Our department (Department of Paediatrics & Adolescent Medicine, Queen Mary Hospital/University of Hong Kong) participated in Phase 1 of ISAAC in 1995, which showed that the prevalence of allergic disorders in school children aged 6-7 years old in Hong Kong was comparable to that in Singapore and Great Britain [9]. We then participated in Phase 3 of ISAAC in 2001, which showed there had been a significant increase in prevalence of severe asthma symptoms, life-time rhinitis, current rhinitis, and life-time eczema and a seeming plateau of life-time asthma, life-time wheeze, and current wheeze [10]. Similar findings were evident in children aged 13-14 years old [11]. We also attempted to explore the change in environmental factors over the period, which was adopted from the environmental module of ISAAC; this may account for the change in prevalence of serve asthma symptoms, life-time rhinitis, current rhinitis, and life-time eczema. Risk factors identified included history of wheezing in parents, male sex, frequent upper respiratory tract infection in early life, and month of birth in locally born girls. However, the increase in prevalence of rhinitis, eczema, and severe asthma symptoms could not be entirely explained by the change of prevalence of the aforementioned risk factors, suggesting that some unidentified factors in Hong Kong might have also contributed significantly to the observed change.

In a subsequent cohort study in 2004, we found that viral infection, a well-known trigger, could account for only a third of asthma exacerbations in 114 children with stable asthma over a 1-year period [12]. Similarly, another local case-control study could only identify significant respiratory pathogens in half of the children admitted for asthma exacerbations [13]. We believed that environmental air pollution was a factor for asthma exacerbation. We confirmed our speculation through another study, showing the significant association between air pollution and asthma admission, an indicator for severe asthma among children in Hong Kong [14]. This study was also the first study in the world that showed the relationship between asthma admission with fine particles $PM_{2.5}$, now recognized as an important air pollutant in different parts of the world. Based on this finding, a reduction of ambient levels of air pollutants including NO_2, PM_{10}, and ozone by an average of 50% of those levels recorded during the 6-year study period could have prevented 570 hospital admissions for asthma in children each year. A recent local study also showed that coarse PM (PMc; 2.5-10 microgram aerodynamic diameter) was associated with emergency hospital admissions for respiratory diseases in Hong Kong independent of $PM_{2.5}$ and gaseous pollutants [15]. In Hong Kong, road traffic, together with the “Canyon effect” due to multistory buildings, is a major source of air pollution especially at roadside in Hong Kong. Exposure to traffic emissions is generally unavoidable in children living in urban areas. Epidemiologic studies have reported associations between residential proximity to busy roads and adverse respiratory health outcomes in children, including respiratory symptoms, asthma exacerbations, and decrements in lung function [16]. A local study confirmed that daily particulate air pollution levels (PM_{10}) in children’s living locations derived from surface extinction coefficients (SEC), as measured by satellite and measurements from air pollutant monitoring stations at ground level, were associated with increased odds of having respiratory symptoms (cough or sputum) [17]. In Hong Kong, while exposure to air pollutants in residential areas poses a major concern for child health, it is noteworthy that 20% of 650 primary schools in Hong Kong are situated close to a main road (as defined by the Transport Department), at a mean distance of 20.5 meters [16].

In industrialized countries, children spend more time (up to 80%) indoors, mostly in schools, than in other places except home. Studies in the United States, South Korea, and Europe have shown poor indoor air quality in many schools and its association with short-term and long-term health problems, including both respiratory and non-respiratory issues [18-20]. A local study in the late 1990s showed that particulate matter was a major problem of indoor air quality in five schools being monitored, but there was no attempt to assess its relationship with health indicators in the children attending those schools [21].

It has been more than a decade since Phrase 3 of ISAAC was conducted in Hong Kong. It is important to explore whether or not the prevalence of asthma, AR, and eczema continue to increase in local children. As ISAAC is a school-based type of survey, it will provide a good opportunity to study the air quality in schools and its relationship to health outcomes measured by the survey. We believed that the result may provide additional information for planning of child health care in Hong Kong.

Aims and Hypotheses

Our aim is to (1) examine the prevalence of asthma, AR, and eczema in 4000 school children aged 6-7 years in Hong Kong between 2001 and 2017, and (2) measure air quality at primary schools and explore its relationship with health outcomes measured by the ISAAC survey.

We hypothesize that (1) there has been a significant change in the prevalence of asthma, allergic rhinitis, and eczema in school children aged 6-7 years old from the last survey in 2001, and (2) there is a significant association between air quality at school and health outcomes measured by the ISAAC survey.

Methods

ISAAC Questionnaire

ISAAC is a world-recognized study using a questionnaire to assess respiratory disease. Our research team has already used this questionnaire for several studies in Hong Kong [9,10]. The survey results were comparable with other countries and have been validated in previous studies.

The questionnaire survey will be the same as the study conducted in 1995 and 2001, that is, the same sampling frame, age group, sample size, questionnaire, and translation.

Selection of Subjects

Our focus is on school children aged 6-7 years old in Hong Kong. Every co-educational primary school in Hong Kong will be divided into 18 groups according to district. Then, within each district, each eligible school will be allocated a number, and two schools will be selected from each district using a table of random numbers. Once a school has been chosen, two school grades will be selected based on having the greatest proportion of 6-7 year olds. All classes in the two grades will be included. We recognize that there will be some children outside the specified age range in each class chosen. These children will be included in the data collection excluded from analysis for the international comparison. If a selected school refuses to participate, it will be replaced by another chosen at random. No eligible children will be excluded from the sample. Based on the previous study, 25 schools will provide an adequate number of children to undertake the study. We plan to recruit 36 schools as the class size may have shrunk over the past few years. We estimate that we will recruit at least 4000 participants.

Sample Size and Power Considerations

The prevalence of symptoms of asthma, AR, and itchy rash were 9.4%, 37.4%, and 4.2% respectively in a study population of 4448 in our previous study. A sample size of 4000 will be able to detect annual increase (decrease) of 0.5% (-0.4%) in prevalence of symptoms of asthma and other allergic diseases for at least 5 years after our last study with a power of 90% at the 5% level of significance.

Study Design

This study is cross-sectional. Three 1-page core questionnaires were developed by the ISAAC to ensure comparable information on the basic epidemiology of asthma, AR, and eczema and can be compared temporally and among countries. The Chinese translation of the questionnaire has been standardized. Additional questions are allowed at the end of the core questionnaire to identify potential environmental risk factors. Four new questions will be added to the set of environmental questions used in 2001 to ask for participants' residential location including the floor of the residential building and the amount of time participants spend at school and at home.

The research was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

Timeline

This study will be undertaken in 2015 to 2017. We will conduct a pilot test to test new questions at the pediatric outpatient department of Queen Mary Hospital in Hong Kong. Parents of children attending the clinic will be invited to participate.

Participation

A participation rate of at least 90% will be sought. It is a concern that absent children may be away from school because of asthma or allergies. Therefore, strenuous efforts need to be made to contact these children and offer them the opportunity to participate in the study. Extra questionnaires will be left in each school for the absent students to take home once they return to school. We will remind the school every month for unreturned questionnaires until we receive all answered questionnaires or until the end of the data collection period. In any case where consent has been refused, demographic data (age, sex, ethnic group) from the school will be sought.

Data Handling and Quality Control

The completed questionnaires will not be changed under any circumstances. Data will be entered in the computer exactly as recorded on the completed questionnaire. A coding manual is available from ISAAC so the core questions will be coded in a standard manner. Any changes to data should be done so for an explicit reason and documented and a copy of original data kept. The questionnaire must not be altered for consistency between the stem and following questions. If some questions are left blank on a particular questionnaire, it will be at the discretion of the ISAAC international data center as to whether that questionnaire is excluded for international comparison. We shall be responsible for coding our own data and data entry as well as analysis. Data are entered two times, and the two versions of the dataset will be compared and any differences checked against the original questionnaire. Any inconsistency can be resolved at that time based on the original questionnaire. A copy of data required for international comparisons will be sent to the ISAAC international data center for analysis along with data from other centers.

Procedures

A randomly selected list of schools will be generated. The school secretary of each school will be contacted by telephone and a personalized letter sent. The letter will include a sample of the questionnaire and the information letter (with the consent form attached) to parents/guardians. All contact with the schools, dates of phone calls, dates that letters are sent, and names of all contact people, especially the secretary will be recorded. The school principal will be called 1 week after the letter has been sent to discuss the procedure that would be undertaken for approval to be given.

When permission has been granted, an appointment will be made for the research assistant to visit the school. The school will be instructed to make available a class list with all the children's names, ages, dates of birth, and ethnic origins, if possible.

As part of the study, we will prepare an appropriate number of reminder stickers to put on the bottom of the information letter (eg, "Please return by Friday" or another day), giving them about a week to complete and return the questionnaire to school. Stickers will be prepared for the children as a small token when the questionnaire is returned. On the day of distribution of the questionnaire, we will give a small introduction of the project to members of the school staff. The number of classes and number of students in each class in Primary 1 and 2 must be obtained, as well as the center and school number (center and school numbers can be entered later as long as Step IV is completed). The name of school must stamped onto each

questionnaire (stamp borrowed from school), and the letter to parents enclosed inside the questionnaire (sticker with date of return put on the bottom of the information letter).

Before distribution, we will perform a final check to ensure that the questionnaire has been numbered, and school name stamped, and then prepare bundles for each classroom held with 2 rubber bands (one horizontal and one vertical) and the class room number written on the top of the questionnaire. A sufficient numbers of stickers will accompany classroom questionnaires and a note attached to each bundle of questionnaires, thanking the teacher. The decision when to return to collect the questionnaires will be discussed with the secretary. The timing will be approximately 1 week.

When we return to the school, all surveys will be sorted based on number sequence and marked off on the class list. For the numbers not marked off, another questionnaire will be re-issued using the same process as above, but the survey number will be 2 instead of 1. A stamped self-addressed envelope will be given for the second issues. For surveys returned uncompleted or blank, we will re-issue the survey but put a survey number 2 above the survey number 1. It will be noted on the class lists the surveys not returned and those returned blank, as well as a record of the re-issue date. A few spare stamped self-addressed envelopes will be left with the school secretary, with a request that any questionnaires returned late to the school be mailed back to the researcher/fieldworker. A letter of thanks will be given to the school, and we will advise them that they will be notified of the results when available.

The surveys collected are put into a locked filing cabinet. Any returned by post are checked against the class list and put into the appropriate class by number sequence. At a less pressured time, the surveys can be checked against the class lists for correct date of birth, age, and numbering. Any corrections to demographic data must be recorded. The questionnaire must not be altered under any circumstances.

School Air Quality Monitor

School visits will be conducted during class time in the academic year. Three sets of air quality monitors will be used for each school: two inside 2 different classrooms and another in an open area within the school. Air pollutants will be monitored at each school for 2 consecutive weeks (5 school days per week). One of the classrooms in each grade level (Primary One and Two) in the school will be selected randomly for the placement of the indoor air quality monitors. Concentrations of particulate matter (PM_{10} and $PM_{2.5}$) will be measured using filter-based samples collected by a $PM_{2.5}$ monitor (TSI AM510) charged with a pump. Concentrations of nitrogen dioxide (NO_2), ozone (O_3), and sulphur dioxide (SO_2) will be measured by passive diffusion samplers using nitrogen dioxide monitor (Z-1400XP), ozone monitor ZDL-1200, and sulfur dioxide monitor (Z-1300), respectively. Temperature and humidity data will also be collected. Safe and childproof sampling sites will be ensured and will comply with the rules as prescribed by the International Organization for Standardization [22,23]. Indoor samples will be collected at a height of about 1-1.5 m above the floor, which is the breathing zone inside the classroom. The selected place will not be allowed to be closer than 1 m to a wall, door, or air-conditioner. Furthermore, the indoor sampling site will be selected as far away as possible to the blackboard, taking into account a minimum distance of 3 m. Outdoor samples will be collected on an open playground if available or near the main school gate. This site will be documented. The monitors will be kept at heights of 1.5-2 m above the ground, at a minimum distance of 1 m from the closest building. Class teachers will be invited to fill out a questionnaire about the school building characteristics (eg, floor of the classroom, classroom adjacent to playground or street) and the indoor characteristics of the classroom during the study period (eg, number of students attending class, ventilation habits, such as whether windows are kept open or closed and the average number of times windows are opened to ventilate the classroom, type of blackboard for teaching, the presence of air conditioning). We will go to the school to download the information from the monitor every week for 2 consecutive weeks.

Satellite Data

Satellite data in this study will be taken from the Moderate Resolution Imaging Spectroradiometer (MODIS) sensors aboard two NASA satellites, Aqua and Terra. Data retrievals are done based on a collection of 3 MODIS level 1B data. An algorithm is used to derive aerosol optical depth (AOD) at a resolution of 1 km x 1 km from the MODIS data based on MODIS 2.1-μm reflectance with 99% cloud-free exclusion criteria on pixels [24]. SEC, which represent surface aerosol distribution, are then derived from the AOD data by taking into account the atmospheric moisture level, the boundary layer height as derived from micropulse lidar measurement [25], and surface visibility reports. Ongoing data retrieval and derivation of AOD and SEC have been conducted by Hong Kong University of Science and Technology. The processed data have been continuously extracted by the University of Hong Kong through a Wellcome Trust project in the School of Public Health and are freely available online.

Estimation of Ambient Air Quality at School Year-Round

Our air quality monitors will measure air pollutant levels at each school for 2 consecutive weeks. Association of our outdoor air quality data with SEC and AOD data from NASA satellites and air quality data from the nearest monitoring stations of the Environmental Protection Department (EPD) Hong Kong will be determined. Using this association, we will estimate school outdoor air quality for a whole year. The satellite data from EPD are freely available online.

Estimation of Ambient Air Quality at Residential Locations

We will ask the participants to provide their residential address in the questionnaire. We will then geocode their residential locations into geographical coordinates using Google Maps. SEC and AOD derived from NASA satellite data will be used to estimate the residential ambient particulate air quality based on the residential locations. This information will be used to adjust for the variation of exposure at home. The building floor number will also be asked to estimate the approximate height

from ground level to further adjust for the proximity from road traffic emissions on the ground level.

Data Processing and Analysis

To assess time trend and environmental factors that account for change, any missing answers on the questionnaire will be merged with negative answers in the analysis, according to ISAAC instructions. Statistical analysis will include percentages, odds ratios, 95% confidence intervals, and chi-square tests for comparison of prevalence in 2001 and this study. All data will be calculated using SAS PC. A significance level of $P<.05$ will be used for all analyses.

We will then assess the relationship between school air quality with asthma and AR. For each pollutant, a 10-day mean concentration (mg/m^3) in each classroom will be computed and a three-class variable of exposure (high, medium, or low) will be defined with respect to the tertiles of the concentration distribution in the classrooms, independent of the district. To investigate the impact of air quality in classrooms, health outcomes will include those measured by ISAAC questionnaires. Potential confounders will be assessed through the same environmental questionnaires in 2001 together with some new questions as previously described. These will include age, sex, place of birth, perinatal factors, ethnicity, number of siblings, socioeconomic status as indicated by highest level of maternal education attained, family income, family size, area of living quarter, the type of accommodation, hospital admission for respiratory tract infection in the first year of life and preceding year, passive smoking, parental or maternal history of asthma and allergic diseases, keeping of pets, and type of fuel used for cooking. The newly added questions will help assess average time at home and at school, road traffic on residential street, and presence of air conditioning and indoor air purifiers at children's homes. Exposure of air pollution at home will also be adjusted from the estimation of ambient air quality at residential locations. Between-school and within-school variability (school variance and classroom variance respectively) of the measured indoor pollutants will be estimated using linear models for longitudinal data (SAS MIXED procedure). Comparisons between groups for population characteristics (ie, within or without a certain health outcome) will be made using the Student *t* test for continuous variables and the Pearson chi-square test or exact Fisher test for the categorical variables. To investigate the relationship between each health outcome and each air pollutant, a marginal model will be used [20] taking into account the potential confounders and air quality around residence by satellite data. This model will calculate the adjusted odds ratio for each health outcome at different levels of pollutant exposure. The marginal model parameters will be estimated using the generalized estimating equation approach (SAS GENMOD) with independent working correlation structure using the individual school number as stratum. SAS v.9.1 will be used for statistical analyses. Bonferroni adjustment will be used to reduce type I errors and tackle the multitasking issue. $P<.05$ will indicate statistical significance.

Discussion

Principal Considerations

Our study aims to examine the prevalence of asthma, AR, and eczema in 4000 school children aged 6-7 years in Hong Kong between 2001 and 2017, as well as to measure air quality at primary schools and explores its relationship with health outcomes measured by the ISAAC survey. The result is useful for understanding the prevalence of childhood asthma and allergies and identifies possible risk factors. It is useful for health care planners in estimating the needs of related services and designing possible prevention measures. Association between school air quality and respiratory health if present will help to inform related departments on planning urban land use.

Limitations

With only 2 years scheduled for data collection and a limited budget, the research team could collect aerosol information in each school for only 2 weeks at three different sites. In Hong Kong, most of the schools have installed air conditioners and they are used for most of the year. Therefore, the seasonal difference would be mitigated. To address this critical issue, data collected from the nearest air monitoring station and satellite data would also be drawn to correlate with the data collected from schools to predict the annual indoor air quality and the variation during different seasons.

This is a cross-sectional study; as such, it is limited in its ability to predict future outcomes or detail past changes. Nevertheless, we will compare the result from this study with the 2001 ISAAC study in Hong Kong. As our study focuses on a questionnaire, it is also susceptible to recall bias. Missing data will likely occur, either because of parental refusal or questions being left blank. We will reduce this as much as possible by re-issuing questionnaires and reminding the schools to return missing questionnaires.

Conclusion

We are now approaching the final stage of the study with only a few schools remaining for data collection. We are continually processing the data, and it is anticipated that the result will be available at the end of 2017 or early 2018.

Acknowledgments

The project is funded by the Health and Medical Research Fund.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Reviewers' and Grant Review Board comments on the protocol.

[PDF File (Adobe PDF File), 936KB - resprot_v6i6e106_app1.pdf]

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Abbreviations

AOD: aerosol optical depth
AR: allergic rhinoconjunctivitis
EPD: Environmental Protection Department
ISAAC: International Study of Asthma and Allergies in Childhood
MODIS: Moderate Resolution Imaging Spectroradiometer
NO2: nitrogen dioxide
O3: ozone
PM: PMc; 2.5-10 microgram aerodynamic diameter
SEC: surface extinction coefficient
SO2: sulphur dioxide

Edited by G Eysenbach; submitted 07.03.17; peer-reviewed by KH Lue; comments to author 14.04.17; revised version received 20.04.17; accepted 24.04.17; published 07.06.17.

Please cite as:
Lee SL, Lau YL, Wong HS, Tian L
Prevalence of and Risk Factors for Childhood Asthma, Rhinitis, and Eczema in Hong Kong: Proposal for a Cross-Sectional Survey
JMIR Res Protoc 2017;6(6):e106
URL: http://www.researchprotocols.org/2017/6/e106/
doi:10.2196/resprot.7252
PMID:28592396

Protocol

Identifying Nonclinical Factors Associated With 30-Day Readmission in Patients with Cardiovascular Disease: Protocol for an Observational Study

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of hospitalization in older adults and high readmission rates have attracted considerable attention as actionable targets to promote efficiency in care and to reduce costs. Despite a plethora of research over the past decade, current strategies to predict readmissions have been largely ineffective and efforts to identify novel clinical predictors have been largely unsuccessful.

Objective: The objective of this study is to examine a wide array of socioeconomic, psychosocial, behavioral, and clinical factors to predict risks of 30-day hospital readmission in cardiovascular patients.

Methods: The study includes patients (aged 18 years and older) admitted for the treatment of cardiovascular-related illnesses at the Duke Heart Center, which is among the nation's largest and top-ranked cardiovascular care hospitals. The study uses a novel standardized survey to ascertain data on a comprehensive array of patient characteristics that will be linked to their electronic medical records. A series of univariate and multivariate models will be used to estimate the associations between the patient-level factors and 30-day readmissions. The performance of the risk models will be examined based on 2 components of accuracy—model calibration and discrimination—to determine how closely the predicted outcome agrees with the observed (actual) outcome and how well the model distinguishes patients who were readmitted and those who were not. The purpose of this paper is to present the protocol for the implementation of this study.

Results: The study was launched in February 2014 and is actively recruiting patients from the Heart Center. Approximately 550 patients have been enrolled to date and the study is expected to continue recruitment until February 2018. Preliminary results show that participants in the study were aged 63.6 years on average (SD 14.0), predominately male (61.2%), and primarily non-Hispanic white (64.6%) or non-Hispanic black (31.7%). The demographic characteristics of study participants were not significantly different from all patients admitted to the Heart Center during this period with an average age of 65.0 years (SD 15.3) and predominately male (58.6%), non-Hispanic white (62.9%) or non-Hispanic black (31.8%) The integration of the interview data with clinical data from the patient electronic medical records is currently underway. The study has received funding and ethical approval.

Conclusions: Many US hospitals continue to struggle with high readmission rates in patients with cardiovascular disease. The primary objective of this study is to collect and integrate a comprehensive array of patient attributes to develop a powerful yet parsimonious model to stratify risks of rehospitalization in cardiovascular patients. The results of this research also have the potential to identify actionable targets for tailored interventions to improve patient outcomes.

(JMIR Res Protoc 2017;6(6):e118) doi:10.2196/resprot.7434

KEYWORDS

cardiovascular disease; readmission; socioeconomic status; psychosocial factors; United States; eHealth; observational study

Introduction

High rates of potentially preventable hospitalizations in adults with cardiovascular disease have put enormous strain on the US health care system [1-4]. Hospital administrators and health care providers are now facing increasing pressure to develop prognostic tools to better identify patients at risk of being readmitted after discharge [2,3,5-10]. This study is an interdisciplinary project that will integrate a comprehensive set of socioeconomic, psychosocial, and behavioral factors with clinical factors to develop an effective model to stratify cardiovascular patients at risk of 30-day readmission. The specific aims of the study are twofold: to administer a novel patient survey to collect an array of nonclinical factors that will be combined with clinical factors from patient electronic medical records and to develop risk stratification models to identify key clinical and nonclinical factors associated with 30-day hospital readmissions.

Methods

Background and Significance

Cardiovascular disease (CVD) is the leading cause of hospitalization in adults ages 65 years and older, and readmissions after discharge are common, costly, and often preventable [1-4]. According to the American Heart Association, CVD-related illnesses cost the United States an estimated $204 billion in hospital services and physician fees in 2010 [1]. Recent studies suggest that approximately 25% of older adults with heart failure and nearly 20% of older adults with myocardial infarction (MI) are rehospitalized within 30 days of discharge, and upwards of 40% of patients are readmitted within 6 months [3-6]. Considering the enormous human and financial costs of readmissions, clinical investigators and hospital administrators are facing increasing pressure to develop prognostic tools to identify patients at risk of potentially preventable rehospitalization [11-13]. However, current strategies to predict readmissions have been largely ineffective, and the predictive prospects of many clinical variables have been nearly exhausted [3,7-10,14].

There is now considerable interest in the role of nonclinical factors in predicting early readmission [3,15-19]. However, efforts to identify novel predictors of rehospitalization have been largely unsuccessful, and hospitals continue to struggle with high readmission rates [2,5]. Of the nearly 200 studies on hospital readmissions in cardiac populations, only a handful have considered nonclinical patient attributes and their wider contexts [3,20,21]. The few studies that exist suggest that factors such as income, marital status, depressive symptoms, and living arrangement are significantly associated with readmission or death in patients with heart failure [8,14-16,22,23]. Despite these promising findings, the full scope of nonclinical variables remains relatively undefined and poorly studied. Consequently, almost nothing is known about how patients' social resources, relationships, and behaviors outside of the hospital impact recurrent hospitalizations.

We propose to use a patient survey to identify the nonclinical characteristics of patients at Duke Heart Center. To our knowledge, this will be the first effort to integrate an array of socioeconomic, psychosocial, behavioral, and clinical factors to identify CVD patients at risk of rehospitalization. This project will lay the groundwork to help develop an effective tool to stratify cardiac patients at risk of rehospitalization prior to discharge and ultimately lower readmissions by identifying key patient characteristics that are associated with poor outcomes and markers for aggressive intervention.

Ethics Approval

The study was approved by the Institutional Review Board (IRB) at Duke University Medical Center (protocol ID Pro00051237) and is funded by the Social Science Research Institute at Duke University.

Design and Procedures

The study includes patients admitted for the treatment of cardiovascular-related conditions at Duke Heart Center in the Duke University Medical Center. Over the past 2 decades, Duke's Heart Center has consistently ranked among the leading heart centers in the country (#1 in North Carolina) and is staffed by the nation's top cardiovascular specialists who care for more than 65,000 patients each year. As a top-ranked hospital for cardiovascular care and treatment, the Heart Center's catchment area of patients is large and diverse. Details of existing policies, initiatives, and usual-care practices at Duke University hospitals and the Heart Center (including Duke's cardiac rehabilitation program) are extensive and fully documented elsewhere [24-27]. Duke also maintains and monitors quality scores on numerous indicators for cardiovascular outcomes, health care quality, and patient satisfaction. Cardiovascular care at Duke consistently meets or exceeds national and state averages in a number of areas, including hospital readmissions [28-30]. Additional information about ongoing cardiovascular studies at Duke University and Duke Heart Center can be found elsewhere [24,31,32].

This study will use a standardized survey to ascertain data on a comprehensive array of patient characteristics prior to discharge (see Multimedia Appendix 1). The instrument was developed to capture 5 patient-level domains: (1) patient demographics and background, (2) socioeconomic status and resources, (3) psychosocial resources, (4) health behaviors, and (5) physical and psychological status (Textbox 1).

Textbox 1. Measures ascertained from the patient survey.

Demographic and socioeconomic background:

- Age (date of birth)
- Sex
- Foreign-born status
- Race/ethnicity
- Marital status
- Household size
- Educational attainment
- Employment status
- Health insurance

Psychosocial factors:

- Health literacy
- Self-efficacy toward health
- Positive outlook
- Social support
- Life stressors
- Negative outlook

Behavioral factors:

- Smoking
- Alcohol consumption
- Religious attendance
- Adherence to medications
- Place of care
- Number of hospitalizations

Self-reported health status:

- Self-rated health
- Activities of daily living limitations
- Symptoms according to the Center for Epidemiologic Studies—Depression (CES-D) survey
- Body mass index
- Likelihood of readmission
- Longevity of parents

The survey data will be collected using a brief (5-10 minute) self-administered paper questionnaire. In almost all instances, the questionnaire items were obtained from existing sources and were previously validated and shown to be psychometrically sound [33-43]. The completed surveys will be collected and the information will be entered into a standardized data entry program. The resulting database will then be linked to the patient electronic medical records using MaestroCare/DEDUCE (Duke University) to identify patients' clinical characteristics, hospital readmissions, and mortality (when available).

Data collection will continue until the required sample size for analysis is obtained. There will be no additional contact with patients after the administration of the in-patient survey. Follow-up data collection will be limited to using MaestroCare/DEDUCE to identify the dates of hospital readmissions or mortality. Follow-up information on ambulatory or primary care will not be collected as part of the current study's protocol, which is to identify key patient characteristics at the time of hospitalization that can be used for risk stratification prior to discharge.

The study will include a research assistant (RA) from the Division of Community Health (DCH). The RA has the appropriate background and qualifications to assist with screening for patient eligibility, obtaining informed consent,

administering the survey, and data entry. As required by DCH and the Duke University Health System (DUHS), the RA will adhere to the policies and codes of conduct for DUHS employees and will have completed the required IRB Collaborative Institutional Training Initiative training (eg, informed consent), Duke Human Resources policy training and background check, and confidentiality agreements. Prior to work in the hospital, the RA also will be required to get vaccinated for influenza.

Selection of Subjects

Consistent with Duke's Quality Improvement initiative to identify the best practices for care, we plan to enroll all eligible subjects who are admitted to Duke University Medical Center for the treatment of cardiovascular-related illnesses (*International Statistical Classification of Diseases, 9th Edition* diagnostic codes: 390-459). Eligible subjects will be aged 18 years or older upon admission. Assuming approximately 200 patient discharges per month and a response rate comparable to in-hospital patient satisfaction surveys (≥70%) [15], we expect to enroll approximately 850 subjects during the data collection period. Reliable estimates of power/sample size are difficult to calculate for this study because of (1) the absence of true treatment groups, (2) the large number of potential predictors, and (3) unknown assumptions about the probabilities (and standard deviations) of readmission or death for each of the various covariates. Nonetheless, established methods and literature demonstrate that a sample size of approximately 500 observations and event rates of 10% to 20% should be adequate to obtain robust estimates of readmission [16,17].

Subject Recruitment and Compensation

The study RA will screen for eligibility using the patients' existing medical records (eg, date of birth). The study and RA will be introduced to patients by their health care provider. If patients are interested in participating, the RA will describe the study and its objectives, obtain informed consent, introduce the survey questionnaire, distribute the instrument, and collect the completed surveys. If requested, the RA will allow the subject to review the survey prior to their consent. The RA will be available to respond to patient questions and concerns throughout the consent process and the administration of the survey. Subjects who refuse to participate will be asked for the reason they declined and the RA will record any additional information (eg, age, gender) that may help minimize future refusal rates. No compensation will be provided to subjects.

Consent Process

Consent will be obtained using standardized procedures and a signed consent form (Multimedia Appendix B). Eligible patients will be given the consent form, which can be read to the patient by the study RA and explained as needed. The designated study RA will be available to answer any questions or concerns that may arise related to the consent process or the interview itself. All subjects to be interviewed will be able to give legal consent.

Study Interventions and Risk/Benefit Assessment

The research poses little risk to subjects and requires no interventions or invasive physical procedures. Although there is a small potential risk from loss of confidentiality, the risk of such loss will be minimized. Potential benefits of the study include the knowledge to improve patient outcomes and improve the overall quality of care at Duke Heart Center. Although there are no benefits to subjects, the results of the data collection and analysis will have potentially important implications for current medical practice and developing patient-centered approaches to treatment. Identification of the sociodemographic and behavioral characteristics of patients will be extremely useful for tailoring treatment regimens that go beyond clinical care and therapeutics by explicitly considering patients' social resources, relationships, and environment. The implementation of a viable and effective instrument to quantify nonclinical risks based on the patients' background has enormous potential to improve care and reduce costs associated with transitions of care and recurrent hospitalizations.

Data Analysis and Statistical Considerations

The data will be collected and analyzed only for purposes of scientific research. As such, the data will only be used to generate statistical summaries and aggregated information that do not permit the identification of any individual patient, family, or household, either directly or inferentially. The initial stage of analysis examines the univariate and bivariate distributions of patients to characterize their baseline socioeconomic, psychosocial, behavioral, and functional status prior to discharge using *t* tests (continuous), Mann-Whitney *U* tests (nonnormal continuous), chi-square tests (categorical), and Fisher's exact tests (binary).

The second stage of analysis will examine the factors associated with 30-day all-cause readmissions. The analyses will be conducted in several steps. First, nonparametric Kaplan-Meier plots will be used to examine the associations between the covariates and early readmission (and death). Next, competing-risk hazard models will be used to estimate the unadjusted and adjusted associations between the patient-level factors and 30-day readmissions (accounting for death as a competing risk). The final set of analyses will examine the performance of the risk models based on 2 components of accuracy. First, model calibration will determine how closely the predicted outcome agrees with the observed (actual) outcome. Graphical comparisons will be made and evaluated using Hosmer-Lemeshow chi-square goodness-of-fit tests. Next, model discrimination will be tested using Harrell's c-index to determine the ability of the model to distinguish patients who were readmitted and those who were not [44]. At each step of the multivariate analyses, we will test for interactions among covariates to identify important subgroup variations in risks of rehospitalization. All analyses will be performed using Stata 12.0 (StataCorp LLC).

Data and Safety Monitoring

The study only involves patient interviews and analyses with survey data and existing medical records (via MaestroCare/DEDUCE). Therefore, there are limited patient safety concerns.

Privacy, Data Storage, and Confidentiality

The study data will be kept secure and confidential as required by law. As part of these safeguards, the data will be located and

analyzed within DCH in the Department of Community and Family Medicine. To protect against the risk of loss of confidentiality, the research team will closely follow the procedures approved by the Duke University Medical Center IRB, and the data will be secured in accordance with the privacy and security regulations of the Health Insurance Portability and Accountability Act. The computerized files used for data entry and analysis will be stored on password-protected computers (and networks) in a secure office in the Mutual Building of the DCH. The DCH's computer network is carefully protected by an appropriate firewall and a centralized monitoring system that protect access to study data. Only the principal investigator and RAs will have access to the data. The completed surveys (hard copies) and informed consent will be kept confidential and stored in locked file drawers in the Mutual Building. No participant identifiers will be used in the presentation or reporting of data.

Results

The study was launched in February 2014 and is actively recruiting patients from the Heart Center. Approximately 550 patients have been enrolled to date and the study is expected to continue recruitment until February 2018. Preliminary analyses of study participants were conducted to compare patients currently enrolled in the study with all patients admitted during the study period and describe the preliminary distributions of study participants across key survey measures. Data collection remains ongoing, and the preliminary results presented here are provided for informational purposes for this active study protocol. Table 1 presents comparisons of hospitalized patients enrolled in the study with all eligible patients at Duke Heart Center.

Overall, results show that the 2 patient groups had similar demographic and clinical profiles. Patients enrolled in the study had a median age of 65 years (interquartile range [IQR] 19) and were predominantly male (318/520, 61.2%), non-Hispanic white (336/520, 64.6%), and married (276/520, 53.1%). The major diagnoses of diseases in patients included acute MI (58/520, 11.4%), atrial fibrillation (154/520, 30.3%), heart failure (173/520, 34.0%), hypertension (255/520, 50.1%), and diabetes (143/520, 28.1%). The demographic and disease profiles of patients were not significantly different between eligible and enrolled subjects. However, the initial patients enrolled in the study had a slightly longer median hospital stay than all patients admitted during the study period (5.1 vs 4.0 days, respectively; $P<.001$). The overall distributions of the patient characteristics ascertained from the survey are presented in Table 2.

Table 1. Comparison of enrolled patients with all patients admitted during the study period at Duke Heart Center (distributions were ascertained from patient electronic medical records and include all encounters (n=6880) from the 5387 total patients admitted during this period).

Parameters	All patients (n=5387)	Enrolled patients (n=520)	*P* value
Demographic characteristics			
Age, median (IQR[a])	66 (21)	65 (19)	.098
Male, n (%)	4032 (58.60)	318 (61.2)	.255
White, n (%)	4296 (62.85)	336 (64.6)	.422
Married, n (%)	3722 (54.10)	276 (53.1)	.652
Clinical characteristics			
Cardiovascular diagnoses			
Acute MI[b], n (%)	992 (14.42)	58 (11.4)	.059
Atrial fibrillation, n (%)	1949 (28.33)	154 (30.3)	.353
Heart failure, n (%)	2059 (29.93)	173 (34.0)	.054
Comorbid diagnoses			
Hypertension, n (%)	3489 (50.71)	255 (50.1)	.789
Diabetes, n (%)	2049 (29.78)	143 (28.1)	.421
Length of stay, median, n (%)	4.02 (4.34)	5.11 (6.9)	<.001

[a]IQR: interquartile range.

[b]MI: myocardial infarction.

Table 2. Characteristics of study participants admitted at Duke Heart Center (n=520).

Parameter	Values	Missing
Demographic characteristics		
Age, median (IQR[a])	66 (19)	
Male, n (%)	318 (61.2)	
White, n (%)	336 (64.6)	
Married, n (%)	276 (53.1)	
Lives alone, n (%)	139 (27.2)	8 (1.5)
Socioeconomic characteristics		
High school or less education, n (%)	198 (38.5)	5 (1.0)
Employment status		6 (1.2)
Currently employed, n (%)	104 (20.2)	
Not employed, n (%)	138 (26.9)	
Retired, n (%)	272 (52.9)	
Health insurance		7 (1.4)
No health insurance, n (%)	10 (2.0)	
Medicaid only, n (%)	27 (5.3)	
Medicare, n (%)	333 (64.9)	
Other sources, n (%)	143 (27.9)	
Psychosocial characteristics		
Health literacy (0-3), mean (SD)	2.26 (0.7)	3 (0.6)
Health self-efficacy (0-4), mean (SD)	3.23 (0.7)	3 (0.6)
Social support (0-20), mean (SD)	16.55 (4.0)	9 (1.7)
Life stressors (0-12), mean (SD)	3.07 (2.1)	13 (2.5)
CES-D[b] symptoms (0-24), mean (SD)	7.60 (4.5)	16 (3.1)
Behavioral characteristics		
Smoking history		10 (1.9)
Never smoked, mean (SD)	208 (40.8)	
Past smoker, mean (SD)	249 (48.8)	
Current smoker, mean (SD)	53 (10.4)	
Alcohol consumption		5 (1.0)
Never drinks, mean (SD)	316 (61.4)	
Moderate consumption, mean (SD)	192 (37.3)	
Heavy consumption, mean (SD)	7 (1.4)	
Non-adherence to medication, mean (SD)	105 (20.9)	18 (3.5)
Health-related characteristics		
BMI[c], mean (SD)	30.33 (8.0)	2 (0.4)
ADL[d] disability, mean (SD)	290 (57.4)	15 (2.9)
Diagnosed HTN[e], mean (SD)	255 (49.0)	
Diagnosed diabetes, mean (SD)	143 (27.5)	
Readmission at 30 days, mean (SD)	105 (20.2)	

[a]IQR: interquartile range.

[b]CES-D: Center for Epidemiologic Studies—Depression scale.

[c]BMI: body mass index.

[d]ADL: activities of daily living.

[e]HTN: hypertension.

Results show that large percentages of admitted patients were not married (244/520, 46.9%), lived alone (139/520, 27.2%), had a high school education or less (198/520, 38.5%), and were not employed (138/520, 26.9%). Although the majority of patients were Medicare beneficiaries (333/520, 64.9%), some had no health insurance (10/520, 2.0%) or only Medicaid coverage (27/520, 5.3%). Most patients had a history of smoking, with nearly half who quit smoking (249/520, 48.8%) and 10.4% (53/520) who currently smoke. Most patients reported no alcohol consumption (316/520, 61.4%) and very few reported heavy consumption (7/520, 1.4%). More than 1 in 5 patients (105/520, 20.9%) reported not taking their prescribed medication in the past year.

In terms of health status, patients had an average body mass index of 30.3 and a sizeable percentage of patients had some limitation in activities of daily living (290/520, 57.4%), were diagnosed with hypertension (255/520, 49.0%), or were diagnosed with diabetes mellitus (143/520, 27.5%). Preliminary results also show that approximately 20.2% (105/520) of patients currently enrolled in the study were readmitted within 30 days of discharge. The current readmission rate of study participants is consistent with national estimates for cardiovascular patients and with readmission rates documented at other North Carolina hospitals [29,30].

Overall, preliminary results show that missing data were minimal (≤3%) across measures in the patient survey. Patient enrollment and data collection efforts remain ongoing. Further integration and analysis of the patient clinical data and survey interview data are also currently underway.

Discussion

Summary

Cardiovascular disease is the leading cause of (re)hospitalization in older adults and despite enormous investments and a plethora of research, many US hospitals continue to struggle with high readmission rates [1,2]. The purpose of this paper was to present the protocol for the implementation of a study to identify how a wide array of socioeconomic, psychosocial, behavioral, and clinical factors are associated with risks of 30-day readmission in patients with cardiovascular disease. The results of this interdisciplinary research have the potential to identify actionable targets for tailored interventions to improve patient outcomes.

In 2009, the American College of Cardiology and the Institute for Healthcare Improvement launched the Hospital to Home (H2H) national campaign to reduce readmissions and improve the transitioning of care for individuals hospitalized with CVD [45]. The overarching goal of the H2H initiative is to reduce rehospitalizations in cardiovascular patients by 20% in the coming years. Failure to meet this challenge may result in the loss of Medicare reimbursement for these untimely readmissions. According to recent estimates, more than one-fifth of older adults with heart failure and acute MI are readmitted within 30 days of discharge and almost 40% are rehospitalized within 6 months [3,5,6,45,46]. Mortality rates after discharge are similarly high [5,9,45]. Although studies show that early physician follow-up, counseling, and improved discharge planning can improve patient outcomes and lower subsequent readmissions [4,47,48], these efforts are often unsustainable due to the prohibitive costs of broad interventions. Thus, it has become increasingly necessary to target patients who are at greatest risk of negative outcomes.

Results from this interdisciplinary study have the potential to assist in clinical decision making, improve transitions of care, reduce hospital costs (and reimbursement penalties), and improve the lives of those with CVD. The proposed research will develop an integrated model that can identify the profiles of patients at greatest risk of rehospitalization or death after discharge. Although not all socioeconomic, psychosocial, and behavioral factors are amenable to medical intervention, identifying the key factors—and how they constellate—will provide actionable knowledge that can be used to devise effective approaches to treatment and rehabilitation (Table 3).

For example, patients with low education may benefit from health-literacy programs to improve their ability to understand complex treatment strategies and manage disease. Alternatively, patients who are socially isolated may benefit most from group therapy to enhance rehabilitative efforts and provide social support. It also may be that psychological distress is an underlying cause of excess alcohol, tobacco, or food intake, and efforts to reduce or manage stress may present the widest prognostic value.

This study will help lay the scientific groundwork for implementing a risk assessment tool that will have important implications for medical practice and improving patient outcomes. The goal of this project is to identify key nonclinical risk factors that can then be integrated with known clinical risk factors from patient medical records to produce a fast and accurate method of risk classification prior to hospital discharge. For physicians, a robust prognostic tool will allow them to quickly identify and aggressively treat high-risk patients who may have otherwise gone undetected through standard processes of care. For hospitals, improved patient stratification and targeted care will help lower the significant costs of emergency room visits and rehospitalizations in those with potentially preventable relapses. And for patients, improved risk assessment will not only facilitate the highest level of personalized care but will also provide them knowledge of health risks that go beyond the cautionary litany of poor diet, inactivity, and smoking.

Table 3. Examples of areas for intervention from study results.

Categories	Identified risks	Possible interventions
Socioeconomic factors	Low education	Provide educational resources and instruction (eg, coaches) to improve health literacy to better manage medications and treatment in low-educated patients
Psychosocial factors	Depression	Provide psychological counseling and schedule group meetings to improve coping strategies and social support in depressed patients
Behavioral factors	Physical inactivity	Implement aerobic exercise interventions to improve cardiorespiratory fitness in sedentary patients
Clinical factors	Hypertension	Schedule routine follow-ups and provide access to coaching/tele-coaching programs to monitor blood pressure control and medication adherence in hypertensive patients
Interactive risks	Widowed×Diabetes	Combine routine physician visits with group sessions to monitor diabetes maintenance and provide social support to minimize complications and treatment noncompliance in widowed diabetics
Cumulative risks	≥3 Behavioral risks	Implement behavioral therapy sessions that use support systems allowing patients to self-select behaviors most likely to achieve risk reduction (in number rather than type)

Limitations

We also acknowledge limitations of this study. First, we recognize that the study is limited to patients admitted for cardiac care at Duke Heart Center; therefore, the generalizability of the findings will require further research. Second, the patient survey does not include an exhaustive list of potential factors that may be associated with rehospitalization or other poor outcomes. Rather, the survey includes a wide range of patient characteristics as an important step toward identifying and quantifying major components of patients' nonclinical background (eg, their education, living arrangement, health literacy, social support) to develop real-time and real-world profiles of CVD patients who are most vulnerable during periods of transitional care. Additional research should build on these findings to further identify and refine such factors. Third, preliminary analyses suggest that initial patients enrolled in the study were hospitalized approximately one day longer than patients who were not enrolled in the study—possibly because of the greater opportunity for study recruitment with a longer length of stay (LOS). Analyses during study enrollment will continue to examine potential differences in LOS, and if differences persist, our subsequent readmission models will assess whether such variations have a (moderating) influence on the associations between risk factors and 30-day readmission. Finally, post hoc power analyses will be conducted near the completion of data collection to determine if the number of patients is sufficient to detect significant differences among covariates. If required, an IRB amendment will be submitted to continue patient enrollment.

Conclusion

In sum, the objectives of this study are highly aligned with the National Institute of Health (NIH) mission of improving transitions of care and reducing hospital costs through the identification and quantification of cardiovascular risks. A major goal of NIH and Healthy People 2020 is to understand the social, psychosocial, and behavioral determinants of adverse outcomes in adults with CVD and to reduce the burden of disease in vulnerable segments of the population. A patient-centered model that can effectively identify and stratify those at risk of rehospitalization will have enormous potential to assist in clinical decision making, reduce hospital costs, and ultimately, improve the lives of those with cardiovascular illness. We are confident that the proposed research will significantly contribute to the interdisciplinary science necessary to help achieve these goals.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Patient survey.

[PDF File (Adobe PDF File), 61KB - resprot_v6i6e118_app1.pdf]

Multimedia Appendix 2

Consent form.

[PDF File (Adobe PDF File), 111KB - resprot_v6i6e118_app2.pdf]

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Abbreviations

ADL: activities of daily living
CES-D: Center for Epidemiological Studies—Depression scale
CVD: cardiovascular disease
DCH: Division of Community Health
DUHS: Duke University Health System
H2H: Hospital to Home

IRB: Institutional Review Board
IQR: interquartile range
LOS: length of stay
MI: myocardial infarction
NIH: National Institutes of Health
RA: research assistant

Edited by A McDougall; submitted 01.02.17; peer-reviewed by F Patmon, M Harris; comments to author 04.04.17; revised version received 18.04.17; accepted 05.05.17; published 15.06.17.

Please cite as:
Dupre ME, Nelson A, Lynch SM, Granger BB, Xu H, Willis JM, Curtis LH, Peterson ED
Identifying Nonclinical Factors Associated With 30-Day Readmission in Patients with Cardiovascular Disease: Protocol for an Observational Study
JMIR Res Protoc 2017;6(6):e118
URL: http://www.researchprotocols.org/2017/6/e118/
doi:10.2196/resprot.7434
PMID:28619703

Protocol

Assessment of Active Video Gaming Using Adapted Controllers by Individuals With Physical Disabilities: A Protocol

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Abstract

Background: Individuals with disabilities are typically more sedentary and less fit compared to their peers without disabilities. Furthermore, engaging in physical activity can be extremely challenging due to physical impairments associated with disability and fewer opportunities to participate. One option for increasing physical activity is playing active video games (AVG), a category of video games that requires much more body movement for successful play than conventional push-button or joystick actions. However, many current AVGs are inaccessible or offer limited play options for individuals who are unable to stand, have balance issues, poor motor control, or cannot use their lower body to perform game activities. Making AVGs accessible to people with disabilities offers an innovative approach to overcoming various barriers to participation in physical activity.

Objective: Our aim was to compare the effect of off-the-shelf and adapted game controllers on quality of game play, enjoyment, and energy expenditure during active video gaming in persons with physical disabilities, specifically those with mobility impairments (ie, unable to stand, balance issues, poor motor control, unable to use lower extremity for gameplay). The gaming controllers to be evaluated include off-the-shelf and adapted versions of the Wii Fit balance board and gaming mat.

Methods: Participants (10-60 years old) came to the laboratory a total of three times. During the first visit, participants completed a functional assessment and became familiar with the equipment and games to be played. For the functional assessment, participants performed 18 functional movement tasks from the International Classification of Functioning, Disability, and Health. They also answered a series of questions from the Patient Reported Outcomes Measurement Information System and Quality of Life in Neurological Conditions measurement tools, to provide a personal perspective regarding their own functional ability. For Visit 2, metabolic data were collected during an initial 20-minute baseline, followed by 40 minutes of game play. The controller (balance board or gaming mat) played was randomly selected. A set of games was played for 10 minutes, followed by 5 minutes of rest, and then another set of games was played for 10 minutes, followed by rest. Quality of game play was observed and documented for each set. During rest, the participant completed questions regarding enjoyment. Following the same procedures, the participant then played the two sets of games using the other version (off-the-shelf or adapted) of the controller. The entire procedure was repeated during Visit 3 with the controller that was not played.

Results: Enrollment began in February 2016 and ended in September 2016. Study results will be reported in late 2017.

Conclusions: We hypothesized that the adapted versions of the Wii Fit balance board and gaming mat would produce greater quality of game play, enjoyment, and energy expenditure in persons with mobility impairments compared to off-the-shelf versions.

Trial Registration: ClinicalTrials.gov NCT02994199; https://clinicaltrials.gov/ct2/show/NCT02994199 (Archived by WebCite at http://www.webcitation.org/6qpPszPJ7)

(JMIR Res Protoc 2017;6(6):e116) doi:10.2196/resprot.7621

KEYWORDS

video games; exercise; physical activity; disability; energy expenditure; enjoyment

Introduction

Physical activity options for individuals with physical disabilities are limited, and existing community fitness programs and available exercise equipment are often inaccessible [1]. With these and other existing barriers (eg, transportation, program cost, staff knowledge), individuals with disabilities are more likely to be physically inactive [2-6] and demonstrate higher rates of obesity [7-11] than their counterparts without disabilities. Development of creative strategies by which to actively engage people with physical disabilities in leisure-time physical activity is vital given the high prevalence of physical inactivity and obesity in this population. One option for increasing the amount of physical activity acquired each week is to replace sedentary behaviors during leisure time with active video game (AVG) play [12-14].

Video game play typically requires only simple pushbutton or joystick actions for player engagement. AVGs, on the other hand, also known as exergames, refer to a category of video games in which game play, progress, and scoring require substantially greater levels of body movement. Since their introduction, AVGs have become popular with people of all ages and have been used in home, community, education, and rehabilitation settings to increase physical activity [13,15-20]. Furthermore, a growing body of literature indicates that AVGs show promise as an enjoyable physical activity alternative for individuals with physical disabilities—one that overcomes some of the common barriers to activity participation such as transportation and facility access [21-26].

It is important to determine whether AVGs can provide a level of physical activity commensurate with achieving health and fitness benefits. A few studies have reported that increases in energy expenditure can be achieved during AVG play in people with physical disabilities, more specifically those with mobility impairments such as cerebral palsy (CP) [27-30], spinal cord injury (SCI) [31,32], and stroke [33-35]. A study by Hurkmans et al [27] measured energy expenditure using indirect calorimetry in adults with CP during Nintendo Wii tennis and boxing games. Participants played in a standing position and achieved moderate intensity exercise during both games. Similarly, two AVG studies on ambulatory youth with CP found that participants were able to achieve moderate intensity exercise with various Nintendo Wii games [28-29] as well as Dance Dance Revolution [28]. A case study on two young adults with CP and one with spina bifida in which participants played Nintendo Wii games and Dance Dance Revolution (adapted for arm use) in a seated position found that only light intensity exercise was achieved during gameplay [30]. Another case study on two young adults with SCI measured heart rate during Nintendo Wii boxing in a seated position and recorded moderate intensity heart rate levels [31]. Additionally, a study of adults with SCI compared seated heavy bag boxing and AVG boxing and found participants achieved moderate intensity exercise levels during both types of boxing and reported AVG boxing to be more enjoyable [32]. Using the Borg Scale of Perceived Exertion, adults post-stroke scored a variety of Nintendo Wii and Sony PlayStation EyeToy AVGs played in a standing position as light to moderate intensity [34]. Two other studies on adults post-stroke using indirect calorimetry during Nintendo Wii [33,35] and Sony Xbox 360 [33] found AVG gameplay while standing to produce moderate intensity exercise. Kafri et al [33] also had participants post-stroke play Nintendo Wii boxing in both a standing and a seated position and found that in the sitting position participants approached anaerobic metabolism.

While it appears that AVGs hold promise as a means for improving health and fitness, there are technical issues associated with their access and utility in individuals with more severe physical disabilities. For instance, the studies noted above for individuals with CP and post-stroke were composed mostly of community ambulators with mild to moderate motor impairments. Unfortunately, however, for individuals with mobility impairments, specifically those who are unable to stand, have balance issues, poor motor control, or cannot use their lower body to perform game activities, gaming hardware for AVG play is typically inaccessible or the game itself offers limited play options [22-23]. AVGs using floorpad game controllers (eg, Dance Dance Revolution, Active Life Outdoor Challenge) have obvious accessibility limitations. The quick and precise motions required for successful AVG play using hand controllers (eg, Sony PlayStation Move motion controller, Nintendo Wii remote and nunchuck) limits their use for many people as well. Systems such as the Microsoft Xbox Kinect, which use a camera-based controller, also pose problems for successful gameplay, as they typically require the player to be standing for the game to function properly.

Rehabilitation engineers and assistive technology specialists have developed a variety of creative and successful adaptations to game controllers and interfaces that allow people with disabilities to play video games. However, successful adaptations of game controllers to allow people with mobility impairments to play AVGs require not only modifications to allow satisfactory game play but also redesigns to assure that the player with a disability experiences a similar level of energy expenditure. Making AVG hardware accessible for people with physical disabilities offers an innovative approach to overcoming a number of barriers to participation and provides an enjoyable and beneficial physical activity option. Our Rehabilitation Engineering Research Center on Interactive Exercise Technologies and Exercise Physiology for Persons with Disabilities (RERC RecTech) team developed two adapted controllers including an adapted balance board for Wii Fit as well as an adapted gaming mat.

Off-the-shelf (OTS) Wii Fit balance boards are designed for play to occur in a standing position. The small platform area (19.5 inches x 12 inches) is only large enough for a player to stand on with feet approximately shoulder width apart. In addition, because the board uses load cells to detect the player's weight and center of balance, all of the player's weight must bear on the top of platform. This makes the board less responsive to those who require the use of stabilization devices (eg, cane, walker) that bear on the floor around the platform and not usable for someone seated in a wheelchair. Furthermore, to fully engage in gameplay, the player must lean and maintain balance in all directions (forward, backward, side-to-side). To increase the level of usability for those with various forms of mobility

impairment, an adapted balance board was designed to provide a large platform area (40 inches x 38 inches), built-in lateral stabilization supports (ie, handrails), and an adjustable sensitivity for shifting the center of balance.

Like the boards, OTS gaming mats are designed for players who can stand and have little to no lower extremity mobility impairment, having a 3 foot x 3 foot playing surface over which eight controller buttons and two menu buttons are widely distributed. This design poses several issues given that many players with mobility impairments would be better accommodated by playing in a seated position. The large playing surface makes it difficult to reach all of the buttons when seated at a table. Furthermore, the buttons are designed for high actuation force as would be common when used by a standing player, thereby becoming very difficult for use with the hands and/or fingers. In addition, the underlying design of the mat buttons is such that "dead" spots exist in the area of each button, which may not be triggered if a player were to try and depress a button with a couple of fingers rather than a whole foot or hand. To increase the level of usability for players with various forms of mobility impairment, an adapted gaming mat was designed with moveable Velcro buttons that could be positioned more closely to each other, with a gauge for reducing the actuation force required, and elimination of the dead spots resulting in a consistent button response over the entire button area.

Our aim was to compare the effect of off-the-shelf and adapted game controllers on quality of game play, enjoyment, and energy expenditure during active video gaming in persons with physical disabilities, specifically those with mobility impairments (ie, unable to stand, balance issues, poor motor control, unable to use lower extremity for gameplay). The gaming controllers evaluated included off-the-shelf and adapted versions of the Wii Fit balance board and gaming mat.

Methods

Design and Setting

All aspects of the study took place at Lakeshore Foundation in Birmingham, Alabama. Lakeshore Foundation is a community organization that provides physical activity, sport, and recreation opportunities for individuals with physical disability and chronic health conditions. Within Lakeshore is the Exercise and Sport Science Laboratory, which houses a variety of equipment dedicated to comprehensive health promotion and sport science research. For the purposes of this study, participants came to the lab a total of three times.

Participants

Following distribution of a flyer, the project recruitment coordinator answered calls or met with interested individuals. At that time, she reviewed the inclusion and exclusion criteria with them using a screening form to determine if they were eligible to participate. Our aim was to enroll 80 participants (15 youth, aged 10-17 years; 65 adults, aged 18-60 years) into the study. Participants were included in the study if they had a confirmed diagnosis of lower extremity mobility limitation (eg, spina bifida, CP, muscular dystrophy, 1 year post-SCI, multiple sclerosis, stroke, or limb loss) with partial or full use of upper extremities and use of an assistive device (eg, cane, walker, wheelchair) or problems with gait, balance, and/or coordination. Participants were excluded if they had an unstable cardiovascular condition, a visual impairment that interferes with playing video games (eg, complete blindness; inability to read game commands on a 52-inch television screen from a distance of 10 feet), or weighed over 350 lbs including their assistive device.

Procedures

Visit 1

During the first visit, informed consent/assent was obtained and demographic and health history information was documented. We conducted an assessment of each participant's functional ability as described below. In addition, participants were familiarized with the equipment (Cosmed K4b2 portable metabolic system) used for the study and the video games that would be played during subsequent visits. Participants played a portion of or the entire game for all those that would be used during testing.

For assessment of physical function, which was conducted during the first visit, each participant performed 18 functional tasks from the International Classification of Functioning, Disability and Health (ICF) [36,37]. Participants completed each task individually and were scored according to their difficulty in completing the task on a scale ranging from 0-4. As defined in the ICF manual, the scoring was as follows: 0=No difficulty, 1=Mild difficulty, 2=Moderate difficulty, 3=Severe difficulty, and 4=Complete difficulty. The specific ICF tasks selected for use in this study were based on a consensus among the research staff. Following observations during pilot testing, staff selected mobility activities listed in the ICF that had the potential to be required for AVG play (eg, standing, reaching, throwing, and jumping). Tasks were grouped to assess participants' lower extremity function and trunk control, and upper extremity function (Table 1). Scores for upper and lower function were obtained by adding the numeric value received on each of the tasks performed. A higher physical function score indicated less functional ability on the selected tasks. Answer to a single question, one for ambulatory and one for wheelchair use, stood alone to represent general mobility.

Table 1. Select ICF mobility activities assessed to calculate mobility function scores relevant to AVG play for each participant.

Category	ICF code	ICF mobility activity	ICF activity description	Test instructions given to participant
Lower Extremity and Trunk Control				
	d4101	Squatting	Getting into and out of the seated or crouched posture on one's haunches with knees closely drawn up or sitting on one's heels, such as may be necessary in toilets that are at floor level or changing body position from squatting to any other position such as standing up.	"Cross your arms on your chest, and crouch down and touch your buttocks on top of the risers and stand back up. If you can, keep your arms crossed."
	d4103	Sitting	Getting into and out of a seated position and changing body position from sitting down to any other position, such as standing up or lying down.	Participant able to stand: "Please sit down in this chair and then stand back up." Participant unable to stand: "Please lie down and then sit up. Now lie back down."
	d4104	Standing	Getting into and out of a standing position or changing body position from standing to any other position, such as lying down or sitting down.	"Please stand up from the chair and then sit back down."
	d4105	Bending	Tilting the back downwards or to the side, at the torso, such as in bowing or reaching down for an object.	"Please bend forward and reach for the tape."
	d4106	Shifting the body's center of gravity	Adjusting or moving the weight of the body from one position to another while sitting, standing or lying, such as moving from one foot to another while standing.	"Shift your weight over to the left foot (hip if in chair) and come back to the center." Repeat with the right side.
	d4351	Kicking	Using the legs and feet to propel something away, such as kicking a ball.	"Please kick the ball."
	d4500	Walking short distances	Walking for less than a kilometer, such as walking around rooms or hallways, within a building or for short distances outside.	"Walk from this piece of tape to the other one at the end of the room and stop when you get there." Distance is 10 m.
	d4508	Walking other (marching in place)	Not applicable	"While standing bring your knees up to hip level one at a time, like you're walking up really big steps."
	d4552	Running	Moving with quick steps so that both feet may be simultaneously off the ground.	"Run from this piece of tape to the other piece of tape at the end of the room." Distance is 10 m.
	d4553	Jumping	Moving up off the ground by bending and extending the legs, such as jumping on one foot, hopping, skipping, and jumping or diving into water.	"Try to jump over this piece of tape to the other side of the floor." Colored tape on floor, 1.6 inches wide.
Upper Extremity Function				
	d4452	Reaching	Using the hands and arms to extend outwards and touch and grasp something, such as when reaching across a table or desk for a book.	A water bottle is placed on a table. Participant sits just within reaching distance of the table. "Reach for the water bottle and grab it without stepping (rolling) forward."
	d4401	Grasping	Using one or both hands to seize and hold something, such as when grasping a tool or a door knob.	"Please pick the water bottle up and hold it."
	d4300	Lifting	Raising up an object in order to move it from a lower to a higher level, such as when lifting a glass from the table.	"Please pick up the water bottle and raise it above your head."
	d4453	Turning or twisting the hands or arms	Using fingers, hands and arms to rotate, turn or bend an object, such as is required to use tools or utensils.	A water bottle is placed in the participant's hands. "Please remove the lid from the bottle."
	d4454	Throwing	Using fingers, hands, and arms to lift something and propel it with some force through the air, such as when tossing a ball.	A tennis ball is placed on the table directly in front of the participant. "Pick the ball up and throw it."

Category	ICF code	ICF mobility activity	ICF activity description	Test instructions given to participant
	d4450	Pulling	Using fingers, hands, and arms to bring an object towards oneself, or to move it from place to place, such as when pulling a door closed.	The participant stands behind a marked spot on the floor. Using green exercise tubing, the tester hands the grip to the participant. Tester takes up the slack of the tubing but does not create tension in the tubing. "Please grab the hand grip and pull it toward you."
	d4451	Pushing	Using fingers, hands, and arms to move something away from oneself, or to move it from place to place, such as when pushing an animal away.	A rolling chair is placed in front of the participant while they are seated. Tester steps back 4-5 ft and instructs the participant to push the chair away. "Push the chair towards me."
Select d4503 OR d465 depending on primary mode of mobility (ambulatory or wheelchair)				
	d4503	Walking around obstacles	Walking in ways required to avoid moving and immobile objects, people, animals, and vehicles, such as walking around a marketplace or shop, around or through traffic, or other crowded areas.	Three cones evenly spaced in a straight line. "Weave around the cones to the other end and then come back around the cones to the start line." Distance is 10 m. Participant performs this task walking with assistive device (eg, cane, crutches, walker) if needed.
	d465	Moving around using equipment	Moving the whole body from place to place, on any surface or space, by using specific devices designed to facilitate moving or create other ways of moving around such as with skates, skis, or scuba equipment, or moving down the street in a wheelchair or a walker.	Three cones evenly spaced in a straight line. "Weave around the cones to the other end and then come back around the cones to the start line." Distance is 10 m. Participant performs this task using their own wheelchair.

In addition to the functional assessment, participants also completed a series of questions from the HealthMeasures resources [38], which were used as an assessment of the individual's own perspective regarding their functional ability. Questions came from the Patient Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurological Conditions (Neuro-QoL). For adults (18+ years of age), the series comprised questions from PROMIS short-form v1.0 Physical Function 20a and from PROMIS short-form v1.0 Physical Function Samples with Mobility Aid. For youth (10-17 years of age), the questions came from the PROMIS Ped short-form v2.0 Upper Extremity and Neuro-QoL PedScale v1.1 LE Function (Mobility) scales. For adults, the questions asked how difficult a variety of daily tasks (eg, vacuuming, yard work, walking, bathing) were to complete (5-point scale, "without any difficulty" to "unable to do", 14 questions), whether their health limited them in their ability to complete certain activities (eg, carry groceries, strenuous sports, walking a mile) (5-point scale, "not at all" to "cannot do", 6 questions), and could they stand and move with and without support ("yes" or "no", 1 question; 5-point scale, "without any difficulty" to "unable to do", 10 questions). For youth, questions asked how difficult a variety of daily tasks (eg, get dressed, open school binder, bend, reach, walk, get on and off low chair) were to complete (5-point scale, "with no trouble" to "not able to do", 28 questions).

Visits 2 and 3

Visits 2 and 3 consisted of exercise testing to assess energy expenditure during AVG play. Upon arrival for these visits, participants were set up with the Cosmed K4B2 portable metabolic system and a Polar heart rate monitor to assess pulmonary gas exchange and indirect calorimetry. Data collection began with a 20-minute rest period to measure resting energy expenditure. For the rest period, participants sat quietly with no speaking or distractions besides light reading of a magazine or viewing their mobile phone. Next, gameplay began with continued Cosmed data collection.

The Nintendo Wii video game console was used for gameplay, with 3 separate video game discs including 1 video game disc for the Wii Balance Board (Wii Fit Plus, Nintendo) and 2 video game discs for the Wii Gaming Mat (Active Life Explorer and Active Life Outdoor Challenge, Bandai Namco Entertainment). Four game sets were created as outlined in Tables 2 and 3. The sets of games played on the balance boards are presented in Table 2, and those played on the gaming mats are presented in Table 3. The games selected for use in this study were chosen in an effort to provide moderate level physical activity during gameplay.

Table 2. Description of each AVG played using the OTS and adapted balance boards.

Mini games	Description
Wii Fit Plus: Set A	
Rhythm Kung Fu	The participant follows the Kung Fu movements of avatar characters in time with the rhythm. Movements include left and right punches, two hand punches, and left and right kicks.
Rhythm Parade	The participant marches in place to the rhythm of the parade while directing the parade with arm movements in coordination with the game.
Obstacle Course	The participant marches in place to run the character through an obstacle course of swinging balls, moving platforms, and jumps.
Bird's-Eye Bull's-Eye	The participant flaps their arms and moves their body to fly through the course landing on targets spread across the map.
Wii Fit Plus: Set B	
Island Cycling	The participant marches in place on the board to pedal the bike throughout the map while capturing flags that are spread across the island.
Penguin Slide	The participant catches fish by leaning left and right on the balance board to control the avatar.
Hula Hoop	The participant rotates their trunk/hips in a circular motion on the board to control the avatar hula hooping.
Ski Slalom	The participant skis down the slope by leaning left and right to control the avatar skiing the course.

Table 3. Description of each AVG played using the OTS and adapted gaming mats.

Mini games	Description
Active Life Explorer: Set C	
Crocodile Stomper	The participant steps on or hits the crocodiles on the game by pressing the corresponding mat button.
Air Plane Panic	The participant steps on or hits the button prompts as they fly an airplane across a course.
Kraken Battle	The participant steps on or hits the button prompts as they fight a kraken in attempt to defeat the boss.
Mummy's Tomb	The participant runs in place to escape the mummy as the character attempts to escape with the gold.
Jungle Vine Ruins	The participant runs in place and jumps to navigate the character through the ruins.
Active Life Outdoor Challenge: Set D	
Sprint Challenge	The participant runs in place to sprint and finish the course.
Jump Rump	The participant jumps in place to control the character jump roping.
Conveyor Belt Runner	The participant runs in place and jumps over obstacles to navigate the character through the course.
Log Leaper	The participant jumps in place to control the character jumping over the logs.
Hurdles	The participant runs in place and jumps to navigate the character through the hurdles.

The controller (Wii balance board or gaming mat), version of the controller (adapted or OTS), and order of the game sets (Board: Game Set A or B; Mat: Game Set C or D) were determined by the participant drawing one of two small pieces of paper out of a cup, which had a number on it (1 or 2). At the start of the second visit, the participant would first draw a number out of the cup to determine which controller (balance board or gaming mat) they would use for that visit. The non-selected controller was played on the subsequent visit. After placing the number back in the cup, the participant would then pull a number to determine which version of the controller they would play first (adapted or OTS). Finally, the participant would draw a number to determine which game set (Board: Set A or B; Mat: Set C or D) they would play first. For the gaming mat, whichever game set was selected first would be played on both versions of the mat (adapted and OTS), and then the second game set would be played on each version. For the balance board, which was difficult to switch between versions because of connectivity and being time consuming, participants played the two set of games on one version (adapted or OTS) and then played on the other version. For each session, gameplay consisted of four 10-minute sets with a rest period of 5 minutes after each game set (Table 4). Visit 3 consisted of the same protocol using the controller that was not played during the previous visit, with numbers drawn for order of play regarding version of the controller and game sets. Data collection for each visit took approximately 75 minutes as follows: baseline energy expenditure 20 minutes; gameplay 4 sets x 10 min=40 minutes; rest periods between games 3 periods x 5 minutes=15 minutes.

Table 4. Example of randomized AVG play during balance board session.

Controller	Activity	Time (minutes)
Adapted Balance Board	Gameplay: Set B	10
	Rest	5
Adapted Balance Board	Gameplay: Set A	10
	Rest	5
OTS Balance Board	Gameplay: Set B	10
	Rest	5
OTS Balance Board	Gameplay: Set A	10
	Rest	5

During gameplay, research staff observed and rated ability to use the game controller (mat or board) and quality of gameplay during each visit. Ability to use the game controller assessed the participant's difficulty/ease of using the controller as required for the game and was rated on a scale of 0-5 (0=Unable, 1=Extreme difficulty, 2=Severe difficulty, 3=Moderate difficulty, 4=Mild difficulty, 5=No difficulty). To assess quality of game play, research staff considered the participants' degree of general game manipulation and user actions as prompted by the game in comparison to how a gamer without a physical disability would play. Quality of gameplay ranged on a scale from 0-5 (0=Unable, 1=Poor, 2=Fair, 3=Moderate, 4=Good, 5=Excellent). Two research staff worked together for all testing sessions, both recorded scores for quality of gameplay and controller usage, and came to a consensus for the final scores at the end of the session. All sessions were videotaped, so in the event that testers could not come to a consensus, the recording would be available for review.

At the end of each game set, participants reported their rating of perceived exertion on a scale from 0-10, with 0=Not Tired at All and 10=Very, Very Tired. During rest periods, participants completed a feedback survey that included the Physical Activity Enjoyment Scale (PACES) [39]. The PACES includes 16 statements such as "I enjoyed it," "It was very exciting," "I felt bored," and "It was no fun at all." All items were rated by the participant on a 5-point scale ranging from 1=Strongly Disagree to 5=Strongly Agree. After reverse scoring 7 items, a final score was computed by calculating the average of the 16 items.

Results

Enrollment started in February 2016 and ended in September 2016. Study results will be reported in late 2017. Outcomes of interest include quality of game play, enjoyment, and energy expenditure. As part of the data analysis, paired comparisons using parametric paired *t* tests will first be conducted. If assumptions of normality are violated then the use of nonparametric tests will be explored. In addition, regression models will be fit that account for covariates such as age and gender. We will evaluate if there is an effect modification by including interaction terms for gender and age. If there is no statistical significance at .05 level for effect modification, an adjustment will be made for these covariates and findings reported based on models that include age and gender as main effects. All statistical testing for prespecified analyses will be conducted at .05 level. Additional post-hoc comparisons will also be conducted and reported. The original *P* value and number of comparisons computed will be reported so that appropriate multiple testing can be performed.

Discussion

Principal Considerations

AVGs can provide a fun and engaging activity for improving health and fitness; however, there are technical issues associated with their access and utility for individuals with physical disabilities. The objective of our study is to compare the effect of OTS and adapted game controllers on quality of game play, enjoyment, and energy expenditure during active video gaming in persons with physical disabilities, specifically mobility impairments. The gaming controllers under evaluation include OTS and adapted versions of the Wii Fit balance board and gaming mat.

Limitations

This is an observational study; therefore, inherent limitations exist and findings will not be generalizable to the broader community based on this study alone. All participants were recruited from the membership of a community physical activity and recreation center for individuals with physical disabilities. All participants were to some degree physically active and varied in their experience with AVGs. Although a familiarization period was provided, some degree of game play learning may have been occurring during data collection. In addition, participants played only a select group of AVGs. Therefore, potential differences in enjoyment and energy expenditure between OTS and adapted controllers may not have been fully captured. Future studies should expand the participant recruitment pool, examine a broader range of AVGs, provide a more extensive familiarization period, and compare AVG play utilizing the adapted controllers to other leisure-time physical activities,

Conclusions

We hypothesize that the adapted versions of the Wii Fit balance board and gaming mat will produce greater quality of game play, enjoyment, and energy expenditure in persons with mobility impairments compared to OTS versions. Making AVGs accessible to people with disabilities offers an innovative

approach to overcoming a number of barriers to participation in physical activity.

Acknowledgments

The contents of this paper were developed under a grant from the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR; grant number 90RE5009-01-00). NIDILRR is a Center within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). The contents of this article do not necessarily represent the policies of NIDILRR, ACL, HHS, and one should not assume endorsement by the federal government. Thanks to Whitney Neal and Brandon Kane for their assistance with this project as part of the research staff.

Conflicts of Interest

None declared.

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Abbreviations

ACL: Administration for Community Living

AVG: active video game
CP: cerebral palsy
HHS: Department of Health and Human Services
ICF: International Classification of Functioning, Disability and Health
Neuro-QoL: Quality of Life in Neurological Conditions
NIDILRR: National Institute on Disability, Independent Living, and Rehabilitation Research
OTS: off-the-shelf
PACES: Physical Activity Enjoyment Scale
PROMIS: Patient Reported Outcomes Measurement Information System
SCI: spinal cord injury

Edited by G Eysenbach; submitted 01.03.17; peer-reviewed by S Jeske, K Ng; comments to author 21.03.17; revised version received 04.04.17; accepted 05.04.17; published 16.06.17.

Please cite as:
Malone LA, Padalabalanarayanan S, McCroskey J, Thirumalai M
Assessment of Active Video Gaming Using Adapted Controllers by Individuals With Physical Disabilities: A Protocol
JMIR Res Protoc 2017;6(6):e116
URL: http://www.researchprotocols.org/2017/6/e116/
doi:10.2196/resprot.7621
PMID:28623186

Original Paper

Modern Innovative Solutions in Improving Outcomes in Chronic Obstructive Pulmonary Disease (MISSION COPD): A Comparison of Clinical Outcomes Before and After the MISSION Clinic

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Abstract

Background: Chronic obstructive pulmonary disorder (COPD) affects over 1 million people in the United Kingdom, and 1 person dies from COPD every 20 minutes. The cost to people with COPD and the National Health Service is huge – more than 24 million working days lost a year and the annual expenditure on COPD is £810 million and £930 million a year.

Objective: We aim to identify patients with COPD who are at risk of exacerbations and hospital admissions as well as those who have not been formally diagnosed, yet remain at risk.

Methods: This mixed-methods study will use both data and interviews from patients and health care professionals. The project Modern Innovative SolutionS in Improving Outcomes iN COPD (MISSION COPD) will hold multidisciplinary carousel style clinics to rapidly assess the patients' COPD and related comorbidities, and enhance patient knowledge and skills for self-management.

Results: This study is ongoing.

Conclusions: This research will capture quantitative and qualitative outcomes to accompany a program of quality improvement through delivery of novel care models.

(JMIR Res Protoc 2017;6(6):e104) doi:10.2196/resprot.6850

KEYWORDS

COPD; chronic obstructive pulmonary disorder; United Kingdom; patient questionnaires

Introduction

Epidemiology of COPD and Prevalence Gap

In the United Kingdom, 1 million people have diagnosed chronic obstructive pulmonary disease (COPD), which accounts for 25,000 deaths annually [1], making it the 5th commonest cause of death and 2nd largest cause for hospital admissions. Annual health care expenditure on COPD is £810 million [2] (equivalent to £1.3 million per 100,000 population). Severe, exacerbation prone COPD costs ten times more to treat than mild disease. COPD causes 24 million lost working days annually, more than any other respiratory condition, costing the economy £3.8 billion [2]. Worse still, cases of COPD will increase by more than 30%

in the next 10 years [3], while an estimated 2 million individuals presently remain undiagnosed. Hospital admissions due to COPD have increased by 13% since 2008 [3].

Portsmouth has significantly higher than United Kingdom national averages for prevalence of smoking (main risk factor for COPD), COPD admissions, readmissions, and deaths from COPD (eg, 74.2 vs 51.5/100,000 population) [4]. COPD also contributes to the gap in life expectancy in those living in areas of highest and lowest deprivation confirming significant inequalities [5]. There are still many general practices with a "prevalence gap" between expected and actually diagnosed COPD patients.

The cost burden of COPD to the Portsmouth Hospitals Trust and to the community is high. In 2013/2014, there were 946 hospital contacts for COPD at a cost of £2,176,675. This includes 286 admissions for COPD with respiratory failure—this is associated with a longer length of stay and higher costs of ventilatory support in a high-care environment. In Portsmouth City, there are approximately 4000 patients with a known diagnosis of COPD.

The identification of patients with undiagnosed COPD will lead to an increase in costs in the short term including medication, smoking cessation, referrals to pulmonary rehabilitation, and flu vaccination. However, in the longer term, it will lead to health care savings by preventing acute admissions as the first diagnosis of COPD (15% of COPD diagnosis are made during an acute admission [1]) and slowing disease progression. A case-finding exercise in nearby Southampton increased COPD prevalence in the area by 50% but reduced acute admissions significantly [6].

The goal of Modern Innovative SolutionS Improving Outcomes iN COPD (MISSION COPD) is to target patients who are high risk and severe patients who have a higher chance of admission and especially of admission with respiratory failure.

Mission Copd

MISSION COPD is a quality improvement project funded by the Health Foundation to trial an innovative way of finding and assessing patients with COPD and also case finding new diagnoses of COPD. MISSION COPD will allow swift early specialist multidisciplinary interventions in primary care to diagnose and treat those at greatest risk, consistent with the United Kingdom's National Health Services (NHS) "5-year Forward View", calling for removal of traditional primary and secondary care barriers. MISSION COPD will target COPD patients with risk factors for exacerbations and deteriorating lung function as well potential new diagnoses of COPD.

A Cochrane review published in October 2013 identified 25 randomized controlled trials of integrated disease management interventions in COPD [7]. The Cochrane review concluded that integrated disease management improved quality of life and reduced hospital admissions and highlighted the following areas as important: education/self-management, exacerbation action plan, exercise, psychosocial/ occupational, smoking, optimal medication, nutrition, follow-up, case management, and multidisciplinary approaches.

The MISSION clinics provide all of the important factors identified by the Cochrane review.

Stage 1: Identifying Those at Risk

The GRASP-COPD tool, recommended by NHS-IQ (NHS-Improving Quality) will be used to identify patients in a standardized format from practice computer systems using pre-identified Read Codes. Read codes are codes used by all general practitioner (GP) medical record systems to code contact with patients. These are standard across all GP software platforms (eg, EMIS, EMIS Web, SystemOne, Vision).

High-risk COPD patients will then be identified by criteria including smoking status, prescribed medications, frequent antibiotics, prescription of oral steroids, hospital or emergency department (ED) admissions, lung function, and symptoms. Potential new diagnoses of COPD will be identified by searching for patients over 35 with a smoking history and contact with the practice for respiratory symptoms such as bronchitis. Many patients will have ≥2 risk factors. A specialist nurse will review the results to check that patients meet the criteria and to exclude any patients who are under hospital follow-up. All hospital letters are stored on the GP medical records. An invitation to attend the MISSION COPD clinics will then be sent by GP practices.

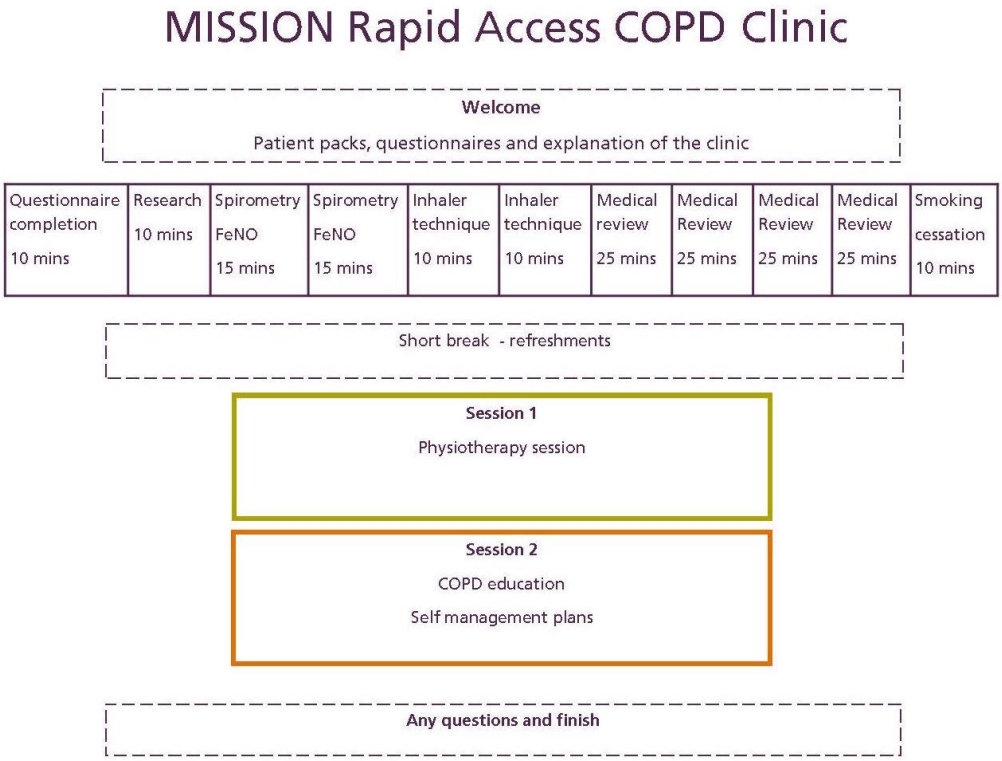
Stage 2: Rapid Access COPD Clinics–Rapid Primary Care Clinics

MISSION Rapid Access COPD Clinics will provide a comprehensive, multidisciplinary assessment of patients with high-risk COPD and not known to secondary care teams, delivered in a carousel fashion at five GP practices on weekends to overcome barriers in accessing health care such as transport and carer availability (see Figure 1).

At each station, the patients will undergo:

- medical review with comorbidity assessment (eg, gastroesophageal reflux, sleep apnea, anxiety, and depression)
- questionnaire assessments of disease control (COPD Assessment Test [CAT]), quality of life (St George's Respiratory Questionnaire [SGRQ]), physical activity (Veterans Specific Activity Questionnaire [VSAQ]), and comorbidity, eg, Hospital Anxiety and Depression Score (HADS), gastroesophageal reflux disease questionnaire (GERD-Q), Epworth Sleepiness Score (ESS) for sleep apnea, and Patient Activation Measurement (PAM) for self-management
- spirometry (FEV1, FVC, FEV1/FVC ratio) and exhaled nitric oxide measurement
- inhaler technique assessment and teaching
- smoking cessation advice and referral where needed
- group education: disease process, exacerbations, treatment options, self-management, pulmonary rehabilitation, and breathing control
- receipt of a personalized MISSION COPD Health Plan (copied to GP) encompassing all relevant information and direct referral for pulmonary rehabilitation if necessary
- invitation to participate in clinical research by research team, if eligible to take part in any studies

Figure 1. RACC Structure.



Stage 3: Severe COPD Assessment Clinics Comprehensive Secondary Care Clinics

Those with severe disease (according to national guidelines) or multiple comorbidities will be invited for further comprehensive review at MISSION Severe COPD Assessment Clinics, again delivered in carousel-style stations, that may include additional full lung function testing, clinical psychology, dietitian, exercise education, medicines use review, social care advice, and same day computerized tomography (CT) scan of the chest, blood test, and echocardiogram. Both clinics will end with an individualized multidisciplinary team assessment of each patient to plan their future care pathway.

Follow-Up

After the MISSION COPD clinics, all patients receive a personalized care plan and the results of the investigations. A copy is also sent to the GP. As part of the service evaluation, a questionnaire will be sent to the patients at 3 and 6 months to measure any change in symptoms or disease control (CAT and SGRQ) as well as self-reported exacerbation history and satisfaction with the clinics. The GP records will be reviewed at 6 months to assess any improvement in exacerbations, hospitals admissions, or GP contact following the clinics.

MISSION COPD Research Study Overview

MISSION is a new and novel way of delivering highly specialized COPD care and has the potential to change the way COPD care across the United Kingdom is delivered as well as services for other long-term health conditions. The MISSION model is the first model of this type, and the current research study aims to evaluate its success.

The study is a mixed-methods evaluation of the new service comparing outcomes before and after the MISSION clinic using data analysis and self-completion questionnaires.

Retrospective quantitative analysis of the data collected during the MISSION clinics will be analyzed looking for COPD phenotypes and contributing comorbidities. The data collected at the initial visit and 3 and 6-month follow-up will be analyzed looking for improvement in COPD control and quality of life following patient attendance at MISSION clinics.

A self-completion questionnaire will be filled in after the clinic by participants in the research study to assess their views on the clinic and where they would like changes to be made. A questionnaire will also be given to health care professionals to seek their views on the clinic.

Qualitative interviews will be conducted with a sample of willing participants to explore the experiences and acceptability of the participants and health care professionals. The interviews with health care professionals will explore their thoughts on MISSION and its strengths and weaknesses as well as any suggestions for improvement.

Study Aims and Objectives

Aims

Our aim is to use quantitative methods to explore the impact of the MISSION service on clinical outcomes and to retrospectively analyze the data collected (as part of their clinical care) from all patients attending MISSION on COPD control, medication usage and technique, exacerbations, comorbidities, allergies, and investigations (blood tests, radiological imaging, lung function). Additionally, we wish to conduct a prospective

qualitative study exploring patients' and health care professionals' views on MISSION.

Primary Objectives

Our two primary objectives of this study are to assess (1) whether the number of COPD exacerbations (prednisolone or equivalent ≥30 mg for >3 days or antibiotics for >3 days) improves in MISSION patients in the 6 months after the clinic compared with the 6 months before and (2) whether hospital admissions change in the 6 months after the clinic.

Secondary Objectives for Patients With Known COPD

For those patients previously diagnosed with COPD, our objectives are to assess the following:

1. whether the number of nonelective GP visits for COPD change in the 6 months after the clinic
2. severity of COPD by Global initiative for Obstructive Lung Disease and British Thoracic Society stage in the MISSION clinics
3. medication and therapy used for COPD in the MISSION clinics and changes made by clinics
4. number of antibiotic courses without prednisolone for lower respiratory tract infections in 6 months before and after MISSION [8]
5. Patient Activation Measure before and after MISSION [8]
6. frequency and severity of comorbidities in the COPD population measured with validated questionnaires (GERD, HADS, ESS) and suspected or confirmed through clinical review
7. COPD control by CAT questionnaire at 3 and 6 months
8. exercise tolerance at 3 and 6 months
9. change in comorbidities at 3 and 6 months
10. inhaler technique – correct technique or correct device
11. lung function and phenotypes of COPD patients seen in MISSION clinic
12. frequency of smoking and referrals for smoking cessation
13. acceptability of MISSION as a service model for patients and staff
14. patient experiences of the MISSION service
15. health economic impact of the MISSION service

Secondary Objectives for Patients With Newly Diagnosed COPD

Additionally, we aim to assess (1) the number of patients with newly diagnosed COPD, (2) how long symptoms were present before diagnosis, (3) frequency of smoking and referrals for smoking cessation, (4) antibiotic history, medication history, and number of contacts with respiratory symptoms prior to diagnosis, and (5) lung function and phenotypes.

Methods

Design

This is a mixed-methods study. It comprises a quantitative analysis of medical records relating to COPD in patients attending the MISSION clinics for baseline health care usage, and further episodes at 3 and 6 months. Self-completion questionnaires will be used to explore participant and health care professionals' views on MISSION using closed and open questions. Qualitative telephone interviews and focus group interviews will be used to explore the experiences and acceptability of patients and health care professionals.

Setting

Data for quantitative analysis will be collected from clinical records made by the clinical team during the MISSION clinics and follow-up questionnaire assessments. GP records will be entered as usual by GP practices. The self-completion questionnaire will be completed by participants in the MISSION research study at the end of the MISSION clinic visit.

Participants will also be invited to give their views on MISSION in a one-to-one interview. The interviews will be held after the clinic by telephone within 2 months of the clinic. Health care professionals will be invited to take part in group interviews at the end of the clinic.

Participants

Participants will be patients who attend MISSION COPD clinics, identified as having uncontrolled or potentially severe COPD or unrecognized COPD from GP records by the MISSION clinical team or health care professionals who attend the clinic in a clinical capacity. Each patient will act as their own control, with their disease control pre- and post-MISSION clinic providing the comparator data [8].

Inclusion Criteria: Patients

The participant must meet all of the following criteria to be considered eligible for the study: male or female, aged 18 years or above; attended the MISSION clinic as a patient; and participant is willing and able to give informed consent for participation in the study. The participant may not enter the study if unable or unwilling to give consent.

Inclusion Criteria: Health Care Professionals

The participant must meet all of the following criteria to be considered eligible for the study: male or female, aged 18 years or above; attended the MISSION clinic as a health care professional; and participant is willing and able to give informed consent for participation in the study. The participant may not enter the study if unable or unwilling to give consent.

Sample Size

All 150 patients who are booked to attend the MISSION COPD clinic will be invited to take part in the study. All health care professionals from primary and secondary care who attend the clinics in a professional capacity will be approached for participation in the self-completion questionnaire and group interview.

The sample size was based on comparing the number of exacerbations in the 6-month period before and after the MISSION intervention. Based on clinical experience, we expect the number of exacerbations in the "pre" period to be approximately 1.0. It is conservatively assumed that the standard deviation of the differences in number of pre- and post-exacerbations will have an equivalent value (ie, SD 1.0).

A clinically important improvement would be obtained post intervention if the number of exacerbations reduced by a third

of an exacerbation (ie, on average, one in three patients had one fewer exacerbations). Using a 5% significance level and 90% power, it is calculated that 97 subjects are required for the study.

It is estimated that two-thirds of available patients will agree to participate and complete the study. Therefore, to obtain the calculated number of patients, approximately 150 patients will be approached to participate. This is approximately the same number of patients who are likely to attend the MISSION clinics.

Recruitment

Patients

All patients who are booked to come to the MISSION clinic will receive a MISSION COPD Participant Information Sheet (PIS) with their booking letter. They will be sent this letter at least a week prior to the appointment.

At the end of the MISSION COPD clinic, all patients will be asked if they wish to enroll in the study and will be given the opportunity to ask questions. If they wish to take part, they will be consented by a member of the research team who will be at the MISSION COPD clinic.

Health Care Professionals

Health care professionals who attend the MISSION clinics (excluding the research team) will be sent a PIS in advance of the clinic. The initial contact and PIS will be made by a clinical administrator rather than the PI or CI. If they wish to take part, they will be consented by a member of the research team at the MISSION COPD clinic.

Screening and Enrollment

Quantitative Data

All patients who attend the clinic will be approached for consent having received a PIS prior to the clinic. They will be given the opportunity to discuss the study with a member of the research team and, if they wish, will be able to take the consent form away and send it back in a stamped addressed envelope. If a patient takes the consent form away to fill in at home, they will be contacted by telephone after 2 weeks as a reminder. If at this point they do not wish to take part, they will not be contacted for the study again.

Patients who attend will be asked to fill in follow-up questionnaires at 3 and 6 months by mail. All participants will be asked to complete a self-completion questionnaire on their experience and views of the MISSION clinic (eg, how they feel managing their COPD, do they get enough support from GP/hospital/practice nurse, how they rate the MISSION clinic with free text for comments).

Qualitative Data

Patients

All patients will be approached for consent having received a PIS prior to the clinic. They will be given the opportunity to discuss the study with a member of the research team and, if they wish, will be able to take the consent form away and send it back in a stamped addressed envelope. If a patient takes the consent form away to fill in at home, they will be contacted after 2 weeks by telephone as a reminder. If at this point they do not wish to take part, they will not be contacted for the study again.

All participants in the study will be invited to take part but may not be selected for interview as we will select on the basis of multiple variation using a grid to map (for example) representation of male/females, age range, job status, and new or existing diagnosis of COPD. We anticipate that there will be up to 30 interviews.

Health Care Professionals

All health care professionals will be approached for consent having received a PIS prior to the clinic by email or post. The PIS will be sent by a clinical administrator rather than the Principal Investigator or Chief Investigator. They will be given the opportunity to discuss the study with a member of the research team.

All health care professionals will be asked if they wish to take part in a focus group meeting at the end of the clinic to discuss positives and negatives of the clinic, any improvements, and any suggestion for development in the future. All health care professionals who wish to take part will be included. There will be approximately 11-20 health care professionals at each clinic from both primary and secondary care. An approximate target of 20 health care professionals has been set (three per clinic) with no maximum or minimum number set.

Ethics

The study will not be initiated before the protocol and all study relevant material such as informed consent forms and participant and GP information sheets have received approval from the Research Ethics Committee (REC), and the respective NHS Research & Development (R&D) department. Any changes to protocol or relevant study documents will be approved by the Sponsor. Should an amendment be made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor amendments, as defined by REC as nonsubstantial amendment, may be implemented immediately, and the REC will be informed.

The study staff will ensure that participant anonymity is maintained. The participants will be identified only by initials and a participant ID number on the Clinical Record Form and any electronic database. All documents will be stored securely and only accessible by study staff and authorized personnel. The study will comply with the Data Protection Act, which requires data to be anonymized as soon as it is practical to do so.

The study will be performed in accordance with the spirit and letter of the Declaration of Helsinki, the Good Clinical Practice Guidelines, the protocol, and applicable local regulatory requirements and laws.

All study staff must hold evidence of appropriate Good Clinical Practice training or undergo Good Clinical Practice training

prior to undertaking any responsibilities on this trial. This training should be updated every 2 years in accordance with trust policy.

Discontinuation/Withdrawal of Participants

Participants may withdraw at any point in the study during the 6-month follow-up period.

Definition of End of Study

The end of study is the date of the last data collection from GP record or participant questionnaire 6 months after recruitment.

Interventions

The participants will have attended a new service, the MISSION clinics, but the care they receive will be no different to standard care according to local and national guidelines.

The difference of the MISSION clinic is (1) the active case finding of patients who are not already known to secondary care but are potentially uncontrolled or who are not known to have COPD and (2) the model of the clinic. Patients seen at the Rapid COPD Assessment Clinic only will undergo more extensive testing and review of their COPD than primary care can provide and will have their comorbidities identified and treatment changes made appropriately.

Patients attending the Severe COPD Assessment Clinic are seen and undergo multidisciplinary review and investigation. The review includes full lung function, inhaler technique, and medical review for all patients and physiotherapy, dietitian, oxygen assessment, CT chest or sinus, psychologist, and smoking cessation as required. Participants will continue to receive their standard treatment.

Quantitative Data Collection

Patients

Notes review will be performed after the MISSION clinics to collect the following data. Where information is not written in medical notes or clinic letters, it will be marked as not assessed. Information will include:

- medical history including COPD history, triggers, allergy history, past medical history, family history, occupation
- lung function
- medication history including COPD and non-COPD medication for comorbidities and related conditions
- exacerbation history including number of steroid courses, hospital admissions, and intensive treatment unit admissions
- health care usage including nonroutine GP attendances, out-of-hour contacts, and ED attendances in 6 months before and after MISSION SAAC or outpatient clinic
- smoking status and if current smoker, whether any smoking cessation advice or referral given
- inhaler technique (if on inhaler) – whether checked, any improvements made, and recommendations for inhaler devices
- comorbidities assessed
- exercise tolerance (using VSAQ plus clinical history)
- questionnaires (PAM, SGRQ, CAT) at baseline and 3 months for all patients
- questionnaires (VSAQ, PAM, CAT, SGRQ, HADS) at baseline and 6 months for patients attending Severe COPD Assessment Clinic
- questionnaires (PAM, CAT, SGRQ) at baseline and 6 months for patients attending Rapid Access COPD Clinics

All participants will be given a self-completion questionnaire, which will be developed in conjunction with Patient Public Involvement advisors.

The areas covered will include the participants' views about their COPD as well as their views on MISSION using a combination of questions with Likert-scale responses and free text answers. The results will be analyzed for content themes and descriptive statistics such as percentages. The questions may include, for example:

- How confident do you feel managing your COPD?
- How was the education and care from GP/hospital/practice nurse?
- How satisfied were you with the booking process for the clinic / the information that you were given/the team that welcomed you?
- Would you recommend the clinic to family and friends?
- What would you like to change about the clinic?
- Has the clinic improved your knowledge of COPD?

Health Care Professionals

All health care professional participants will be given a questionnaire, which will be developed in conjunction with a Patient Public Involvement advisor. The areas covered will include their views on MISSION, problems, barriers, and positive experiences, as well as their experience of COPD care, education, and areas of good practice and areas for improvement using Likert scales and free text answers.

Qualitative Assessment

Patients

All patients will be asked if they wish to have a short one-to-one interview (approximately 30 minutes) to give their views on the clinic. The interview will be held by a member of the research team, and the participant will be invited to say anything they would like to about the clinic. Interviews will be held by telephone within 2 months of the clinic visit.

Health Care Professionals

All health care professionals will be asked if they wish to attend a group interview at the end of the clinic to give their views on the clinic. The interview will be facilitated by a member of the research team, and the health care professionals will be invited to say anything they would like to about the clinic they have just taken part in.

Qualitative Data Analysis

The interviews will be digitally audio recorded and transcribed by a professional transcription company. The data will be entered into a software program to facilitate qualitative analysis (NVivo10). All participants' names will be removed from the transcripts to retain confidentiality. When writing the results, quotes will be used that represent key themes in the data. However, no quotes will be directly attributed to participants.

The data from open-ended questions will be entered into NVivo10 to facilitate qualitative analysis. All participants' names will be removed from the data to retain confidentiality. When writing the results, no quotes will be directly attributed to participants.

The results from the questionnaires and interview will be analyzed using a thematic and framework analysis that uses a 5-step approach to analyzing and writing up data [8]. This involves familiarization with the data, identifying themes, indexing the themes onto the data, charting, and mapping the themes. The themes from the patient and health professionals' questionnaires and interviews can be compared. This will enable key themes to be systematically identified and to map the themes from the patients against those from the health care professionals.

Patient Public Involvement

The MISSION project was developed by members of the clinical team at Portsmouth after the experience of seeing patients in clinic. MISSION COPD has been developed after a successful MISSION asthma project and feedback from patients who attended.

A patient advisor will review and give feedback on all patient-facing documentation for the study. A patient volunteer will be invited to review the PIS and give advice and feedback on the qualitative questionnaire.

Patient volunteers and patients who have taken part in the study and express interest will be invited to help with dissemination events. The results will be submitted for presentation at national conferences.

All study participants will be given a summary of the study results in an appropriate format.

Results

The results will be submitted for publication in summer 2017.

Discussion

Principal Considerations

COPD affects over 1 million people in the United Kingdom and 1 person dies from COPD every 20 minutes [1]. The cost to people with COPD and the NHS is huge—more than 24 million working days a lost a year and the annual spend on COPD is £810 million [2].

Portsmouth has a higher rate of smoking, which is the commonest cause of COPD, as well as a much higher rate of death caused by smoking than the average for England [4]. Over 900 people were admitted to Portsmouth Hospitals NHS Trust because of COPD in 2013/2014.

The aim of MISSION COPD is to reduce hospital admissions and improve peoples' quality of life. A project in Southampton where a team looked for people with undiagnosed COPD reduced hospital admissions even though they increased the number of people with a diagnosis of COPD [6].

Our clinics will find patients with severe COPD or with undiagnosed COPD and review them in a one-stop clinic held at their GP surgery—a Rapid Access COPD Clinic. Patients who need more tests will then be seen at a Severe COPD Assessment Clinic at the hospital. Our goal is to see if patients who come to the MISSION clinics have an improvement in their COPD symptoms in the 6 months after the clinic compared to the 6 months before the clinic.

All patients who come to the MISSION COPD clinic will be asked to participate in the research. There are two parts to the research – data analysis and interview. All patients will be invited to take part in both parts, but not everyone will have an interview. Data will be collected from the notes and entered onto a record form anonymously, which will then be analyzed. Interviews will be held over the telephone at a time convenient to the participant. Health care professionals will be invited to take part in a focus group interview at the end of the clinic.

Strengths and Limitations

This is a small study that will establish the feasibility and successes of the MISSION project. As such, it is not powered for statistical significance. However, its small size allows for greater review of the process through staff and patient experiences allowing the model and project to be changed for future delivery.

Conclusion

This research is important as it will provide evidence to support the use of the MISSION clinic model for patients with COPD. It will also give us more information on patients with COPD and any medical conditions related to their COPD so that we can adapt our service to meet their needs. The telephone and group interviews will help us understand what we are doing right and what we are doing wrong with COPD care.

Acknowledgments

This study was sponsored by Portsmouth Hospitals NHS Trust and funded by Health Foundation and Pfizer. The lead fellow was supported by Health Education England – Wessex.

Conflicts of Interest

None declared.

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Abbreviations

CAT: COPD Assessment Test
COPD: chronic obstructive pulmonary disease
CT: computerized tomography
ED: emergency department
ESS: Epworth Sleepiness Score
FEV1: forced expiratory volume in 1s
FVC: forced vital capacity
GERD-Q : Gastroesophageal Reflux Disease Questionnaire
GP: general practitioner or general practice
HADS: Hospital Anxiety and Depression Score
MISSION: Modern Innovative SolutionS Improving Outcomes iN
NHS: National Health Service
NHS-IQ: NHS-Improving Quality
PAM: Patient Activation Measure
PIS: Participant Information Sheet
R&D: Research and Development
REC: Research Ethics Committee
SGRQ: St George's Respiratory Questionnaire
VSAQ: Veterans Specific Activity Questionnaire

Edited by G Eysenbach; submitted 24.10.16; peer-reviewed by N Unciano, D Ryan; comments to author 28.01.17; revised version received 30.03.17; accepted 04.04.17; published 05.06.17.

Please cite as:
Lanning E, Roberts C, Green B, Brown T, Storrar W, Jones T, Fogg C, Dewey A, Longstaff J, Bassett P, Chauhan AJ
Modern Innovative Solutions in Improving Outcomes in Chronic Obstructive Pulmonary Disease (MISSION COPD): A Comparison of Clinical Outcomes Before and After the MISSION Clinic
JMIR Res Protoc 2017;6(6):e104
URL: http://www.researchprotocols.org/2017/6/e104/
doi:10.2196/resprot.6850
PMID:28583907

Original Paper

A Web-Based Data Collection Platform for Multisite Randomized Behavioral Intervention Trials: Development, Key Software Features, and Results of a User Survey

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Abstract

Background: Meticulous tracking of study data must begin early in the study recruitment phase and must account for regulatory compliance, minimize missing data, and provide high information integrity and/or reduction of errors. In behavioral intervention trials, participants typically complete several study procedures at different time points. Among HIV-infected patients, behavioral interventions can favorably affect health outcomes. In order to empower newly diagnosed HIV positive individuals to learn skills to enhance retention in HIV care, we developed the behavioral health intervention Integrating ENGagement and Adherence Goals upon Entry (iENGAGE) funded by the National Institute of Allergy and Infectious Diseases (NIAID), where we deployed an in-clinic behavioral health intervention in 4 urban HIV outpatient clinics in the United States. To scale our intervention strategy homogenously across sites, we developed software that would function as a behavioral sciences research platform.

Objective: This manuscript aimed to: (1) describe the design and implementation of a Web-based software application to facilitate deployment of a multisite behavioral science intervention; and (2) report on results of a survey to capture end-user perspectives of the impact of this platform on the conduct of a behavioral intervention trial.

Methods: In order to support the implementation of the NIAID-funded trial iENGAGE, we developed software to deploy a 4-site behavioral intervention for new clinic patients with HIV/AIDS. We integrated the study coordinator into the informatics team to participate in the software development process. Here, we report the key software features and the results of the 25-item survey to evaluate user perspectives on research and intervention activities specific to the iENGAGE trial (N=13).

Results: The key features addressed are study enrollment, participant randomization, real-time data collection, facilitation of longitudinal workflow, reporting, and reusability. We found 100% user agreement (13/13) that participation in the database design and/or testing phase made it easier to understand user roles and responsibilities and recommended participation of research teams in developing databases for future studies. Users acknowledged ease of use, color flags, longitudinal work flow, and data storage in one location as the most useful features of the software platform and issues related to saving participant forms, security restrictions, and worklist layout as least useful features.

Conclusions: The successful development of the iENGAGE behavioral science research platform validated an approach of early and continuous involvement of the study team in design development. In addition, we recommend post-hoc collection of data from users as this led to important insights on how to enhance future software and inform standard clinical practices.

Trial Registration: Clinicaltrials.gov NCT01900236; (https://clinicaltrials.gov/ct2/show/NCT01900236 (Archived by WebCite at http://www.webcitation.org/6qAa8ld7v)

(JMIR Res Protoc 2017;6(6):e115) doi:10.2196/resprot.6768

KEYWORDS

iENGAGE; software design; behavioral research; survey; Web application; HIV; user perspective

Introduction

In multisite behavioral intervention trials, participant enrollment, randomization, data collection, security, storage and access, and intervention fidelity are all components critical to the success of a study [1,2]. However, recruitment activities for multisite trials are challenging [3]. Meticulous tracking of study data must begin early in the study recruitment phase and must account for regulatory compliance, minimize missing data, and provide high information integrity and reduction of errors [4,5]. Central study coordinators are typically tasked with tracking and documenting participant activities [3,4]. Electronic data capture is a necessity for multisite randomized clinical trials and is replacing the practice of manual data entry on paper forms [4]. There are several electronic data capture systems available for the conduct of randomized clinical trials, and while there are some examples of behavioral sciences research being supported by software [2], this practice is much less common than in the clinical trials space. Like most randomized clinical trials, in behavioral intervention trials, participants typically complete several study procedures at different time points. Prior studies indicate that a single coordinator may simultaneously work on more than one study and customized study software solutions that allow accurate tracking and documentation of encounters are needed [4]. With limited literature available on multisite behavioral intervention trials supported by custom software, there is little opportunity for such investigators to learn how this technology could facilitate the accomplishment of their research goals.

Among HIV-infected patients, behavioral interventions can favorably affect health outcomes. In particular, the events of the first year after diagnosis are critical to achieve favorable long-term health outcomes. While patients adjust to a new diagnosis, they must develop behavioral skills to simultaneously fully engage and remain in HIV care longitudinally [6]. Adherence to HIV primary care appointments and antiretroviral therapy (ART) during the first year is associated with achieving clinical care milestones like HIV viral load (VL) suppression [7], a marker of effective HIV therapy, and decreased mortality [8,9]. In order to empower newly diagnosed individuals living with HIV to learn skills to enhance retention in HIV care, we developed the behavioral health intervention Integrating ENGagement and Adherence Goals upon Entry (iENGAGE) funded by the National Institute of Allergy and Infectious Diseases (NIAID). In this trial, we deployed an in-clinic behavioral health intervention in 4 urban HIV outpatient clinic sites in the United States. In order to scale our intervention strategy homogenously across 4 US clinic sites, we to developed software for this study that would function as a behavioral sciences research platform.

We identified a need to develop a Web-based platform to collect and maintain data uniformly and to serve as a resource for interventionists implementing a behavioral science intervention to improve outcomes during the first year of HIV care. In this manuscript, we aimed to (1) describe the design and implementation of a Web-based platform to facilitate the deployment of a multisite behavioral science intervention; and (2) report on the results of a survey to capture end-user perspectives of the impact of this platform on the conduct of a behavioral intervention trial.

Methods

Overview iENGAGE

iENGAGE is a National Institutes of Health (NIH)/NIAID-funded (R01 AI 103661) in-clinic behavioral intervention trial designed to evaluate intervention efficacy relative to standard of care for improving treatment outcomes among patients initiating HIV medical care. This multisite randomized controlled trial (RCT) implemented a comprehensive intervention arm that combines 2 previously tested approaches—Centers of Disease Control (CDC) Retention in Care (RIC) [4] and Participating and Communicating Together (PACT) [5] to support the establishment of early behaviors that help patients to arrive at scheduled medical appointments and learn to take ART medications as prescribed.

Setting

The implementation sites were the University of Alabama at Birmingham (UAB), the University of North Carolina at Chapel Hill (UNC), Johns Hopkins University (JHU) in Baltimore, and the University of Washington in Seattle (UW). The institutional review boards (IRB) at each participating site approved this protocol.

Study Team

The research team consisted of a principal investigator (a physician with more than 20 years of research experience), a study coordinator, 2 research assistants, and 2 interventionists. The software development team consisted of a senior designer (a physician with more than 20 years of research experience), a network and security expert, 2 programmers, and a data analyst.

The UAB/overall study coordinator was integrated into the informatics team and became a regular participant in software development meetings, also serving as a liaison to the principal investigator and the site coordinators at UNC, UW, and JHU. The overall study coordinator was empowered by the principal investigator to have final approval of changes to the software to facilitate study workflow.

Software Development

Software development took place within the UAB Research and Informatics Service Center (RISC). We used a user-centered design approach and integrated the overall and UAB iENGAGE study coordinator and coordinator responsible for study implementation across the 3 other study sites into the software development process. Initial meetings focused on cementing the understanding of the study protocol and means to conduct the intervention evaluation uniformly across the 4 sites.

We developed iENGAGE as a Web-based application using C# and .NET, which use a 128-bit encryption Secure Sockets Layer (SSL) certificate to protect any data transmitted to or from the application and all user passwords were hashed into the user table. This Web-based application is accessible from any computer and does not require local installation. Each user across the 4 US HIV clinics, can access the software with their distinct user name and password, and embark on real-time data capture at the point of care (ie, exam rooms before or after physician visit) via the Internet-connected device of the user's choice (eg, laptop, tablet, desktop, etc). Keeping participant confidentiality in mind, we made every effort to include minimal protected health information (PHI) and securely host data in UAB Health System Servers using the Oracle Relational Database Management System (RDMS). Apart from being an informational data repository, this Web application actively informs workflow by firing alerts at scheduled times for study activities for enrolled patients [10,11]. Our design had to accommodate screening, enrollment, and intervention activities during total study duration.

We defined the key features for the software after extensive and repeated discussion with stakeholders at various times. The first series of discussions began before grant submission, when we met with the principal investigator, participated in the initial study design, and collaboratively conceptualized the overall features the software would need to incorporate to support the planned intervention. After the grant was funded, regular meetings with the study team took place. During these meetings, the research team finalized the proposed study workflow, while the design of the software needed to support the intended data collection was prototyped concurrently.

The following is a list of key features needed to support multisite behavioral sciences research that arose from these meetings: (1) study screening and enrollment, (2) participant randomization, (3) real-time data collection by study personnel and participants, (4) facilitation of longitudinal workflow, (5) reporting, and (6) reusability.

Study Screening and Enrollment

Upon initiating the enrollment of a potential study participant under the “Registration” tab, users accessed a “screening form” specific to the iENGAGE study that included questions that comprised the study inclusion and exclusion criteria (Figure 1). Once the screening form was completed and saved, the software would inform research staff if the participant was eligible or ineligible to participate in the iENGAGE study. Upon successful screening, a study-specific identifier was automatically assigned to each participant (Figure 1). This centralized method of data collection on recruitment activities ensured consistency across study sites.

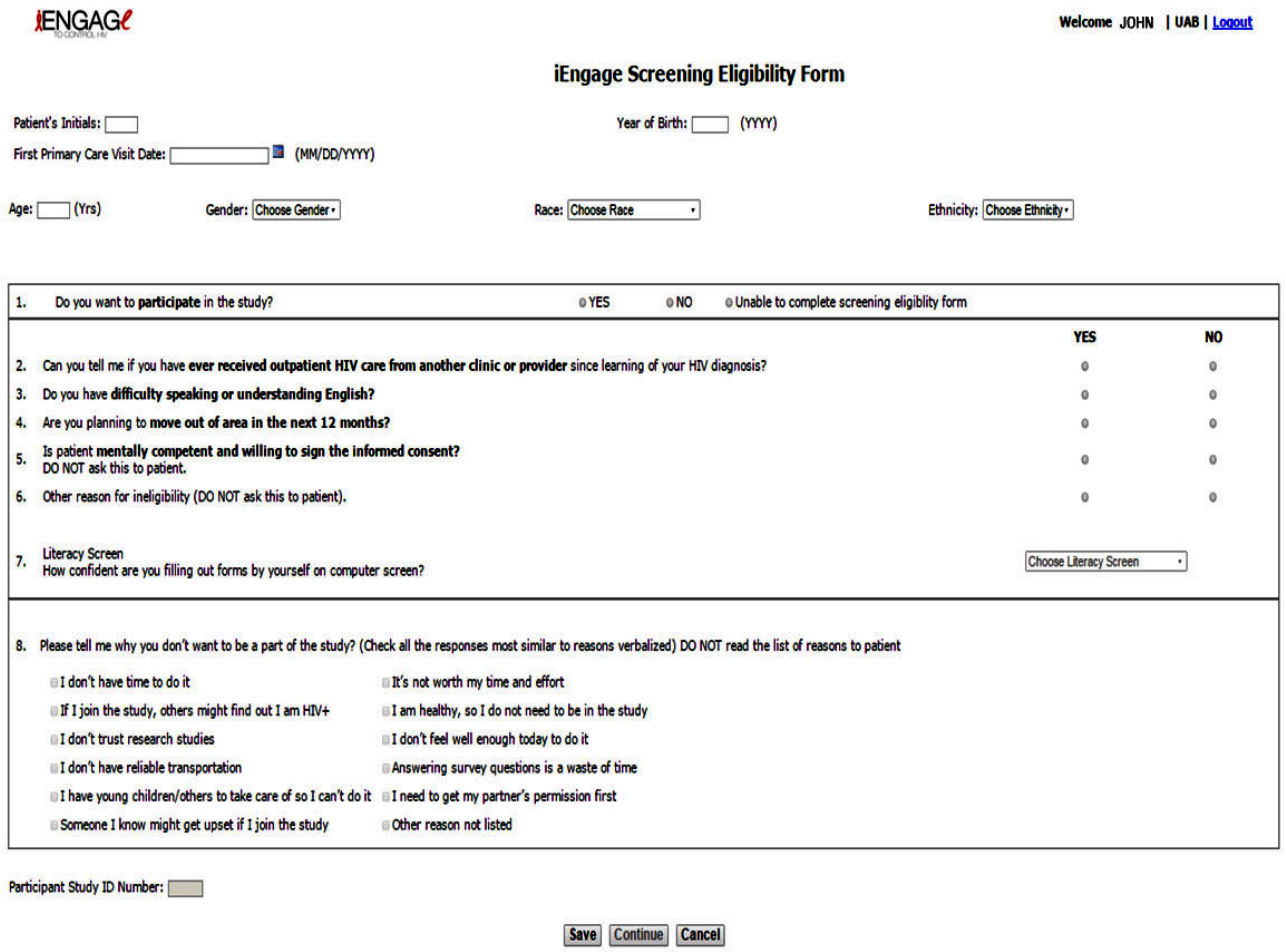
Participant Randomization

In order to randomize participants equally to study arms across all sites, randomization took place centrally. We used a variant of the permuted block randomization process to complete randomization to a specific study arm (intervention or control) in a 1:1 ratio [12]. First, we used third party statistical software (SAS) to generate a list of random numbers in blocks of 2, 4, or 6 that were loaded into a randomization table in our software. As each participant was enrolled in the study, the next (externally) generated number in the random sequence would come up and, depending on the value, the participant was assigned to the intervention or control arm of the trial. This approach of electronically pre-loading a random sequence of numbers generated by the study team in a statistical software solution of their choice provided our researchers greater facility in regards to our participant randomization process, while at the same time eschewing the need to create code to randomly assign study participants to an arm of the study. This solution allowed for subsequent reusability and customization to varying study sizes.

Real-Time Data Collection

The need for real-time, in-clinic capture of information was an important part of functionality. This impacted design and the user experience, necessitating an interface optimized for tablets and continuous Internet connection. This allowed study personnel mobility throughout the clinic and supported interaction at the point of care.

Figure 1. Patient registration.



For this behavioral intervention trial, the research team created specific forms for data capture that supported the intended study design and subsequent analyses for inclusion in the software. These study forms included close-ended (eg, single answer "Yes"/"No" or multiple choice questions) and open-ended questions (ie, "Other, please specify") supported via free text fields within our software. These free text fields supported the capture of unplanned and/or unexpected data for subsequent review by our investigators.

Facilitation of Longitudinal Workflow

It was imperative that researchers across multiple sites followed a single study protocol longitudinally. By understanding the study protocol and its timeline, we were able to design forms triggered by the passage of pre-specified time intervals from enrollment that would appear in a study coordinator's worklist automatically. Thus, study coordinators did not have to individually track when participants were due for subsequent interventions and/or contacts (eg, final assessment 12 months after enrollment). In addition, a flag that changed colors from green to yellow to red when a form was overdue accompanied each new form. These functions facilitated both patient tracking throughout the study and contributed to the timeliness of data collection.

Reporting

The software was able to generate pre-specified data reports upon request that would allow evaluation of enrollment milestones from each study location as well as indicating for each participant their location on the study protocol timeline. We pulled data on a recurring monthly basis to conduct audits on the study status at each of the 4 sites. These reports facilitated both site-specific and central monitoring of fidelity and adherence to study protocol, by indicating cases where the study protocol was not being met and triggering appropriate and timely action. In case of additional ad hoc data requests, our study coordinator submitted a formal query form detailing requested data elements to the informatics team at UAB. Such ad hoc requests could potentially be added as pre-specified reports if needed.

Data was provided in Microsoft (MS) Excel, MS Access, and comma-separated values (CSV) files a format that could be imported into various available statistical analysis software packages (eg, SAS, STATA, etc).

Reusability

A key principle of our design was reusability. As our group supports multiple ongoing behavioral science studies, we strove to build functionality that would support this line of research. Thus, we focused our design on features that would provide flexibility to support future study protocols, such as

customizable worklists, reporting, and participant randomization functions.

This software has positively impacted our behavioral science researchers. By utilizing Web-accessible software to support behavioral science, research stands to greatly benefit participants and investigators as it allows for data capture outside of clinics in patient's homes and community settings and supports a branch of research that has had limited access to such tools in contrast to clinical trials. This software also benefits participants by empowering those that, due to disability or other limitation, cannot participate in research in traditional clinical settings. In fact, we have used this database for other ongoing behavioral intervention trials like Birmingham Access to Care (BA2C) and will be using it in other projects for community testing and linkage to care for HIV, hepatitis C, and sexually transmitted infections in 2017.

Testing

We implemented database testing initially at UAB during which we performed a variety of study activities using the software.

During the initial round of testing all UAB (ie, central site) users (N=5) completed a round of one-on-one testing of the software and reported findings to the development team. During testing, each prospective user added fictional participants (equal to or greater than 1) to the database and completed the forms associated with the study with the goal of following study workflow from enrollment to completion. The research team users provided feedback directly to the software development team. We reviewed proposed changes with the study coordinator, and once approved, made these changes to the initial software prototype. A second round of testing at UAB involved a user group simultaneously following a fictional participant from enrollment to study conclusion. Representatives from the software development team attended this session and collated feedback for subsequent review with the study coordinator. From this second round, we added additional iterative changes to the software and it was deemed ready for external testing.

External testing was divided into 2 rounds; a one-on-one round followed by a group session by all external users (N=8). We collated feedback from each round and reviewed with the study coordinator who had final approval of proposed changes to the software.

Study recruitment started at UAB and served as a 1-month pilot period that allowed further software testing during real-world workflow conditions. Before we started the study recruitment procedures at UAB, all major changes were completed. At this point, we can say that there were no major changes made to the database. Before launch, each participating site took part in an online webinar to provide training on new functionality. We collected feedback continuously from each site by the central study coordinator who communicated with the development team in regular meetings, which led to further refinements in software functionality as appropriate. There were some minor front-end changes to the user interface that included some fields for data collection per the request of the additional 3 participating sites once they had started recruiting.

Additional Features, Roles, and Functionality

This Web application supported multiple simultaneous users. We defined several user types and their corresponding access depending on their study roles (eg, research assistants, study coordinators, and interventionists). We assigned users a discrete user name and password to login. Once logged in, the home screen displayed tabs to register and search for enrolled participants. The "Registration" tab allowed users to complete the screening activity for potential participants that determined if a participant was eligible, or ineligible, for the iENGAGE study, assigning a study identification (ID) for the former. The "Search" tab allowed users to search for already registered participants and look at all the completed forms. This allowed for a quick review of a participant's study-related history.

We designed the worklist to provide a clear and easily accessible task list. It differed slightly for team members depending on their roles in the study (eg, research assistants, study coordinators, and interventionists). For research assistants and study coordinators, it displayed a summary of participants screened, their status on the study at that point, along with upcoming study activities for each participant (Figure 2). For the interventionists, the worklist presented pending tasks among intervention arm participants shortly before they were due, minimizing the chance of intervention activity deviations to maximize fidelity in delivery.

Figure 2. Worklist.

Data Quality and Security

We introduced features in our design to enhance data quality wherever possible and minimize subsequent data cleaning on the back-end. For example, we pre-populated fields with pre-existing data as much as possible to avoid duplication of effort and prevent transcription errors (eg, participant ID and enrollment date). Field controls (date or response ranges) and mandatory fields and/or form completion where indicated by the study team were added. For instance, intervention sessions had mandatory forms like a risk screener and a face-to-face appointments form; users could not move to the next session unless they completed all required forms for the prior session. Once the forms were saved on the system, users were not allowed to make edits. Administrative rights were required to make any changes to the database and all such changes were made centrally. This Web-based application was designed in a way that each user had a unique username and password to login to the website. Therefore, multiple users could access the software simultaneously but not using the same account. No user could override recorded data. In case a documentation error was recognized, our policy was to communicate and clear the issue with the study coordinator and the principal investigator. Thus, only requests approved by the principal investigator and clearly representing a data entry error were changed while data collection was ongoing.

Data are stored and maintained on secure UAB servers where other health system patient data are housed. Data were backed up daily and security updates were made in a timely manner regularly to ensure appropriate protections of the database. Data queries privileges were granted only to a RISC data analyst who was accessible to investigators.

Survey Development and Data Collection

We adopted a user survey from the Web quality instrument published by Aladwani et al to design the iENGAGE research database Web application survey [13]. This 25-item instrument was structured to evaluate user perspectives on research and intervention activities specific to the iENGAGE trial and overall performance of the iENGAGE platform. There were several questions that all study team members responded to and few of which focused solely on research and intervention activities, which were restricted, based on user roles on the study (ie, research staff versus interventionists).

The initial set of questions focused on appearance (ie, color and fonts), adequacy (ie, always up and available with search and navigate options), specific features (ie, tracking study activities and color code schemes), and data collection procedures (ie, accuracy, patient registration, enrollment, and randomization process, up to date participant information, and data organization and security). Another set of questions asked users if it was meaningful to participate and provide feedback in developing this application. We assessed if pilot testing made it easier to understand user responsibilities and if users would recommend involving research team members in designing Web-based applications in future studies. These items were measured using a 7-point Likert scale from 1 (strongly disagree), 2 (disagree), 3 (disagree somewhat), 4 (undecided), 5 (agree somewhat), 6 (agree), to 7 (strongly agree). We assessed general overall experience and satisfaction using a scale ranging from very negative (0%) to very positive (100%). A set of open-ended questions asked users to list the most and least useful feature of the Web application and users shared their opinions on whether there was something that they would like to change or add. We asked users to provide their suggestions and/or recommendations for future improvements. In addition, we asked users with previous experience of using research software

applications to compare iENGAGE to those previously utilized. We implemented this paper-based survey to all software users' at all 4 study sites. A Portable Document Format (PDF) of the survey was sent to all users via email. Users either completed this survey by editing the PDF copy or manually completed a printed copy. All surveys were returned via email to the UAB study coordinator. Survey responses were kept anonymous beyond the receiving team member (UAB study coordinator). All surveys returned to UAB were manually entered, merged, and verified using an Excel spreadsheet which was then imported in SAS for analysis.

Quantitative Analysis

We calculated descriptive statistics to present percentages of user agreement for the close-ended questions. We calculated agreement of user survey responses where "agreement" is defined as a composite measure of strongly agree, agree, and agree somewhat.

For open-ended questions, we consolidated the feedback and described them in the results.

Results

Overall, 372 participants were enrolled and randomized across sites using this Web-based platform in the iENGAGE behavioral intervention trial.

Overall, 13 users completed the survey. Of those, 46% (6/13) were research activity users, 38%, (5/13) were intervention activity users, and 15% (2/13) were using both. We found approximately 90% (≈12/13) overall agreement on the appearance and functionality of the Web application survey (Table 1). There was 100% (13/13) agreement in user responses on ease of use of this database for completing participant registration, enrollment activities, randomization process, and tracking intervention sessions using color code flags (Table 1). All users agreed that the database was accurate in maintaining longitudinal workflow accurately (tracking study activities) and in the organization of participant information (Table 1). Nearly 85% (11/13) of the users agreed that it was easy to track baseline or final study assessments with color code flags (Table 1). All users rated their overall experience, and satisfaction was above 80% on a scale of 0% to 100%, where 0% was negative, 50% was neither negative nor positive, and 100% was positive. There was 100% (13/13) user agreement that participation in the database designing and/or testing phase made it easier to understand user roles/responsibilities and recommended participation of the research team in developing a database for future studies.

In reviewing the responses to the open-ended questions, when users where asked about the most useful features of the application, database users across sites acknowledged ease of use, color flags, longitudinal work flow, and data storage in one location as the most useful features. Users highlighted the registration and randomization processes as user-friendly. Checking eligibility and completing an upcoming task within the assigned study window indicated by the color flags were described as a useful functionality. Users also found maintaining longitudinal workflow in accordance with study protocol and its timeline a useful feature.

Users described some issues saving participant forms, security restrictions, and worklist layout as the least useful features on the database. Some users mentioned that there was nothing least useful on the database. Worklist layout or the order in which participants appear on the worklist and the way ad hoc forms were created as some features that users would like to change in the database to enhance functionality. Users would like to add features like edit options, reminder call tracking, and linkage of the database to the calendar within the software. In addition, one suggestion was to add a feature to capture participant clinic appointment information within the database.

Discussion

Principal Findings

We successfully designed a Web-based platform specifically for a multisite behavioral intervention trial to consistently capture patient participant data and maximize fidelity in intervention delivery. There is little evidence available on measuring quality constructs of Web-based applications [13], and to our knowledge, there is scant literature evaluating software applications developed to support behavioral sciences research. By conducting a survey to capture end-user perspectives and reporting on the impact of our behavioral science research platform on the conduct of this type of research, we provided information on the value and impact of features for end-users. Survey results underscored ease of use, color flags, and longitudinal workflow (tracking study activities) as effective features of the database. In the survey, after the experience of using the software in the conduct of the study, our users suggested ideas to enhance acceptance and study functionality. We believe the capture of such information iteratively with the software's utilization has provided important insights that we have used to strengthen the reusability of our behavioral science research platform software and encourage other developers to connect with their users in a similar fashion.

Table 1. Survey agreement for close-ended questions on the Integrating ENGagement and Adherence Goals upon Entry (iENGAGE) Web application survey (N=13).

Question	Total, n (%)	Agreement (%)				Undecided (%)
		Overall	Strongly agree	Agree	Somewhat agree	
Appearance						
Always up and available	13 (100)	100	62	31	8	
Fonts were properly used	13 (100)	92	46	46		8
Colors were properly used	13 (100)	92	46	46		8
Functionality						
Easy to track study activities (baseline, final assessment) with color code schemes added[a]	8 (62)	88	38	38	13	13
Easy to track intervention sessions with color code schemes added[b]	7 (54)	100	71	29		
Easy to search participants	13 (100)	92	23	46	23	8
Easy to navigate through	13 (100)	100	38	54	8	
Easy to complete patient registration[a]	7 (54)	100	43	43	14	
Easy to complete enrollment activities (enrollment form, CASI[c])[a]	8 (62)	100	50	50		
Easy to complete randomization process[a]	8 (62)	100	50	38	13	
Accurately tracked participant's study activities	13 (100)	100	31	69		
Always up to date with participant information	12 (92)	92	33	50	8	8
Facilitated organization of participant information	13 (100)	100	31	54	15	
Ensured security of participant information	13 (100)	92	46	38	8	8
It was meaningful to participate and provide feedback in the development process of this application as a whole	12 (92)	92	58	33		8
Easy to understand user roles/responsibilities	9 (69)	100	56	33	11	
I will recommend participation of research team in developing a research database application for future studies	12 (92)	100	67	25	8	
Overall experience			≥80	≥90	100	
Please rate your overall experience	12 (92)	25	58	17		
Overall satisfaction			≥80	≥90	100	
Please rate your overall satisfaction	12 (92)	33	42	25		

[a]Only research team answered these questions.

[b]Only interventionists answered this question.

[c]CASI: computer-assisted self-interview.

[d]With participation in the design and testing phase.

Comparison With Prior Work

We believe that integrating research and informatics expertise during the initial database design and final testing phases was an essential step towards successful development of the iENGAGE behavioral research software. Typically, the lead site develops and pilot tests a database, which the collaborating sites have to comply. This could be challenging for the participating sites and interfere with systematic data collection of study activities [14] as factors influencing local use are unknown and may impact implementation. All iENGAGE database users (100% agreement) reported that participation in testing and design phases of the database made it easier to understand user roles/responsibilities on the iENGAGE Web application and recommended participation of the entire research

team in developing a Web application for future studies. Our results highlight that close collaboration of research and informatics professionals on a software development project is critical to success and our process offers insights on tangible approaches to achieve this integration.

Behavioral intervention trials are an important part of research, particularly in the management of chronic conditions where, despite the availability of therapies, important gaps in adherence and implementation continue to negatively impact patients. Developing software to support the deployment of behavioral health studies can change the ways in which such trials are conducted to facilitate achievement of research goals [15]. Moreover, tailoring software and access to the specific roles of a research team in conducting a trial (eg, research activities versus intervention delivery) is paramount to usability and satisfaction. The need for software that is customized to study requirements and provides secure multisite simultaneous access to facilitate data collection, and is designed to be integrated into clinical care settings where participant time is limited, will continue to grow, and its adaptability to these settings will be an important factor for success. Collaborative approaches to software development and the utilization of surveys to elucidate user insights especially after completion of the study protocol are an important source of data to improve subsequent software design and should be used routinely. These insights have proved to be very valuable to our team and have been integrated in subsequent enhancements to our behavioral science research platform. In the future, we would explore the possibility of integrating this behavioral research software to patients' electronic health record (EHR) and allow functionality such as study enrollment directly from the clinical record.

Limitations

The limitations of this study include a relatively small sample size and a limited geographic area (4 sites) in similar urban settings in large academic medical centers; all factors that may have influenced study results. Survey data were collected anonymously, though the anonymity of responses could potentially have been compromised by the limited number of participants. However, we only asked all users to mention their user role on the survey (not any identifiable information) and merged all surveys to present study results. Social desirability bias is also a potential limitation; however, we note that respondents were forthcoming in offering suggestions to enhance the software including current features that were less than optimal.

Conclusion

The development of software applications to support behavioral research will be a key component of gaining insight into improving disease management in the age of population health. The successful development of the iENGAGE behavioral science research platform validated the approach of early and continuous involvement of the research study team working side-by-side with informatics designers and programmers in development. In addition, we recommend the post hoc collection of quantitative and qualitative data from the users after deployment as this has led to important insights on how to enhance our software. These approaches have resulted in a flexible toolset that will be able to support multiple behavioral science research studies going forward.

Acknowledgments

Our study team would like to thank the Research and Informatics Center (RISC) at UAB and the UAB 1917 Clinic personnel for their help with this project. Special thanks to Vara Laxmi Chekkilla and Praneetha Likki for assistance with database development and to the UAB 1917 Clinic Cohort faculty and staff for their assistance with this project. Thanks to Brian Wallace for his assistance with figures. This research received funding from the National Institutes of Allergy and Infectious Diseases (NIAID) (R01 AI 103661).

Conflicts of Interest

JHW has received research support from the Bristol-Myers Squibb Virology Fellows Research Program for the 2006 to 2008 academic years, Pfizer, Tibotec Therapeutics, and Definicare, and has consulted for Bristol-Myers Squibb and Gilead Sciences. AOW has received research support from Definicare. GAB has received research support from the Bristol-Myers Squibb Virology Fellows Research Training Program for the 2010 to 2012 academic years. MJM has received support from Bristol-Myers Squibb and personal fees from Gilead Sciences, Jansen Therapeutics, and Bristol-Myers Squibb, unrelated to the submitted work.

Multimedia Appendix 1

CONSORT EHEALTH Publication form.

[PDF File (Adobe PDF File), 2MB - resprot_v6i6e115_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
ID: identification
iENGAGE: Integrating ENGagement and Adherence Goals upon Entry
JHU: Johns Hopkins University
MS: Microsoft
NIAID: National Institute of Allergy and Infectious Diseases
PDF: Portable Document Format
RISC: Research and Informatics Center
UAB: Alabama at Birmingham
UNC: University of North Carolina at Chapel Hill Baltimore
UW: University of Washington
VL: viral load

Edited by G Eysenbach; submitted 07.10.16; peer-reviewed by N Abdala, K Claborn, T English; comments to author 15.01.17; revised version received 26.01.17; accepted 04.03.17; published 16.06.17.

Please cite as:
Modi RA, Mugavero MJ, Amico RK, Keruly J, Quinlivan EB, Crane HM, Guzman A, Zinski A, Montue S, Roytburd K, Church A, Willig JH
A Web-Based Data Collection Platform for Multisite Randomized Behavioral Intervention Trials: Development, Key Software Features, and Results of a User Survey
JMIR Res Protoc 2017;6(6):e115
URL: http://www.researchprotocols.org/2017/6/e115/
doi:10.2196/resprot.6768
PMID:28623185

Original Paper

Systematic and Iterative Development of a Smartphone App to Promote Sun-Protection Among Holidaymakers: Design of a Prototype and Results of Usability and Acceptability Testing

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Abstract

Background: Sunburn and intermittent exposure to ultraviolet rays are risk factors for melanoma. Sunburn is a common experience during holidays, making tourism settings of particular interest for skin cancer prevention. Holidaymakers are a volatile populations found at different locations, which may make them difficult to reach. Given the widespread use of smartphones, evidence suggests that this might be a novel, convenient, scalable, and feasible way of reaching the target population.

Objective: The main objective of this study was to describe and appraise the process of systematically developing a smartphone intervention (mISkin app) to promote sun-protection during holidays.

Methods: The iterative development process of the mISkin app was conducted over four sequential stages: (1) identify evidence on the most effective behavior change techniques (BCTs) used (active ingredients) as well as theoretical predictors and theories, (2) evidence-based intervention design, (3) co-design with users of the mISkin app prototype, and (4) refinement of the app. Each stage provided key findings that were subsequently used to inform the design of the mISkin app.

Results: The sequential approach to development integrates different strands of evidence to inform the design of an evidence-based intervention. A systematic review on previously tested interventions to promote sun-protection provided cues and constraints for the design of this intervention. The development and design of the mISkin app also incorporated other sources of information, such as other literature reviews and experts' consultations. The developed prototype of the mISkin app was evaluated by engaging potential holidaymakers in the refinement and further development of the mISkin app through usability (ease-of-use) and acceptability testing of the intervention prototype. All 17 participants were satisfied with the mISkin prototype and expressed willingness to use it. Feedback on the app was integrated in the optimization process of the mISkin app.

Conclusions: The mISkin app was designed to promote sun-protection among holidaymakers and was based on current evidence, experts' knowledge and experience, and user involvement. Based on user feedback, the app has been refined and a fully functional version is ready for formal testing in a feasibility pilot study.

(JMIR Res Protoc 2017;6(6):e112) doi:10.2196/resprot.7172

KEYWORDS

sun-protection; sunburn; sunscreening agents; sunbathing; health behavior; health promotion; formative research; intervention

Introduction

Skin cancer incidence within white populations has been increasing worldwide [1-3]. Exposure to ultraviolet radiation (UV) and history of sunburn—both modifiable behavioral factors—are considered the major etiologic factors for melanoma [4-6]. Epidemiologic studies suggest that sun-safe behaviors, such as wearing protective clothes, avoiding sun-exposure at midday, and sunscreen use would decrease the amount of intermittent sun-exposure and have an important effect in reducing skin cancer incidence [7].

Skin cancer is the most common form of all types of cancer diagnosed in the United Kingdom [8]. The age-standardized melanoma incidence rate for 2010 was 17.1 per 100,000 people in the population. In the same year, malignant melanoma was the fifth most common type of cancer [9]. The number of individuals engaging in risk behaviors during their holidays is increasing. Sunburn is a common experience while on holiday [10,11] and sun-related behaviors, such as intentional sun-seeking behavior, are increasingly high [12,13]. In the United Kingdom, studies evaluating effectiveness of sun-protection interventions in recreational settings are sparse. Currently, the SunSmart campaign implemented by the Cancer Research, UK [14], is the major intervention being rolled out.

Considering the time of day and location barriers in interventions designed to target holidaymakers, it seems easy to conclude that interventions that use mobile computing and communication technologies (eg, smartphones and personal digital assistants) are potentially an effective option for skin cancer prevention. Several systematic reviews have demonstrated the potential of mobile technologies to change health-related behavior [15-18]. Text messaging services have been shown to be a valuable strategy in increasing sunscreen use [19] and, more generally, sun-safety behaviors in young Australian adults [20].

One of the main problems identified in a previous systematic review of interventions delivered in tourism settings was the lack of detail on the development process [21]. The Medical Research Council guidance on the development of complex interventions is widely recognized and entails a specific set of processes and methods that will enable replication and transparency [2,3]. The first step, and the target of this paper, is to synthetize the best available and most appropriate evidence that can then be used to inform the specific features of the intervention. A key element in the development of new technologies for behavior change is whether it suits its purpose and meets users' needs and expectations [22]. This information can help intervention developers understand user perspectives on the topic and intervention features, which can maximize the acceptability of the newly developed intervention [23].

A recent study [24] designed and developed a mobile-phone app to promote sun-protection, using a user-centered design. Four rounds of usability testing were implemented by conducting focus groups with 22 potential users. Participants rated the Solar Cell app favorably and described it as being "user friendly." The process of intervention development in this app did not report the use of evidence from recent systematic reviews in the area of skin cancer prevention [21,25,26]. For instance, the intervention could have benefited from using some of the strategies suggested, such as stimulating social norms and providing appearance-based information about photoaging with UV photographs [21].

As identified by a recent systematic review [21], previous studies conducted in the skin cancer prevention area had several shortcomings: (1) measurement procedures (eg, lack of objective measures), (2) study design (eg, mainly uncontrolled before-after), (3) poor intervention description and reporting, (4) lack of systematic development building on established knowledge, and (5) poor description of theory base. One of the gaps in this review was related to the fact that no mobile-phone interventions had been available or tested when the review was completed. According to the Medical Research Council framework [2,3], systematic reviews with behavior change techniques (BCTs) analysis provide a starting point for intervention development. However, there are still uncertainties on how to (1) fill the gaps where the evidence base is limited, (2) establish theory, and (3) engage experts from different fields in the development process.

This paper provides an innovative approach on how to integrate different sources of information in a thorough, systematic, and iterative development process for the *mISkin* app, targeting sun protection. By consistently describing how behavioral interventions are derived and decisions made based on specific constraints, more transparency and reproducibility will be achieved in the area of skin cancer prevention. The main objective of this study is to describe and appraise the process of systematically developing a smartphone based intervention (*mISkin* app) to promote sun-protection during holidays. This process incorporates both theory and evidence-based approaches outlined by the Medical Research Council framework [2,3], engaging users perspectives in the development process of the *mISkin* app [22,23].The specific research questions this paper will answer are as follows: (1) What are the different strands of evidence used to inform the development of the mock-up prototype of the smartphone app? (2) What are the participants' routines during holidays and how can a sun-protection app fit into these routines? and (3) What are the potential app users' reactions to or interactions with a mock-up prototype?

Methods

Ethics

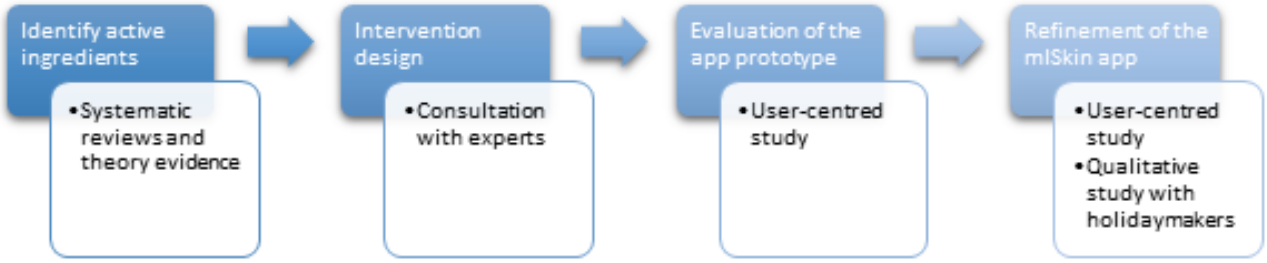
The study was approved by the Faculty of Medical Sciences Ethics Committee (Newcastle University) (Reference no: 00427_2/2013).

Overview

The development process of the *mISkin* app was conducted over four sequential stages (Figure 1): (1) identify evidence on the most effective behavior change techniques (BCTs) used (active ingredients) as well as theoretical predictors and theories, (2) evidence-based intervention design, (3) co-design with users of the *mISkin* app prototype, and (4) refinement of the app. Each stage provided key findings that were subsequently used to inform the design of the *mISkin* app. Figure 1 provides an overview of the sequential stages of the development process.

This section presents the procedures and key findings used to inform the next stage of the iterative development process. A brief summary of the rationale for the development of a smartphone intervention to promote sun-protection during holidays is also provided.

Figure 1. Overview of the stages of the development process for the mISkin intervention.



Stage 1: Identifying Active Ingredients, Behavior Change Theory, and Modes of Delivery Evidence

Procedure

Evidence from a systematic review assessing the efficacy of interventions promoting sun-protection behaviors in holiday settings [21] conducted by the authors and wider evidence for behavior change was synthesized by the research team.

The content of the interventions was coded using a taxonomy of behavior change techniques [27]. Methods of delivery were coded in terms of the format (ie, individual or group/community), content (ie, verbal communication, written material, videos, photographs, interactive activities, and environmental resources), provider (ie, professionals delivering the intervention materials), and setting (ie, location) of the intervention [28].

Analysis

Data from the relevant literature was extracted and collated in a mapping exercise that covered included BCTs and rationale for inclusion. The list of included BCTs and rationale was used to inform the content of the intervention in stage 2.

Stage 2: Consultations With Experts and Intervention Design

Procedure

After gathering, collecting, and analyzing information regarding state-of-the-art evidence, the design and concept development of the smartphone app was informed and overseen by an interdisciplinary group of experts in dermatology, behavior change, and computing science. Experts presented experience in designing, developing, and evaluating theory-based interventions and psychological theories of behavioral change, experience on the cutaneous response to ultraviolet radiation (UVR), and development and application of pervasive computing interactive technologies for health and well-being.

Two main sets of expert consultations were conducted: (1) behavioral scientists plus computer scientists and (2) behavioral scientists plus dermatological science researchers and vitamin D experts. The meetings were frequent during the early stages of app design and initial testing (ie, approximately every month). These were structured by defining clear agenda items beforehand and by keeping detailed minutes of main decisions discussed. After reaching agreement over the overarching themes and design, the meetings with app developers were regular to evaluate the progress of the app design.

Analysis

Translating the interventions content into app features involved repeated iterations between members of the research team conducting the systematic review of the current available evidence and the members of the team with expertise on app development. The initial step was to agree on the theoretical basis and principles underpinning the intervention based on previous studies. This evidence informed the production of guiding principles that described the key features to be included in the app. These discussions also explored the best ways to deliver the BCTs selected and the agreed guiding principles for the intervention. After reaching an agreement over the key app features and design, we met regularly to evaluate progress of the app design.

Data retrieved from these discussions were collated to develop interactive mock-ups and a workflow for the *mISkin* app.

Stage 3: Evaluation of the mISkin App Prototype

Participants

A total of 17 adults (13 females) aged 21-62 years (mean=36.8, SD=11.3) participated in the semistructured interviews. Participants were recruited through advertisement leaflets placed across Newcastle upon Tyne, United Kingdom.

Procedure

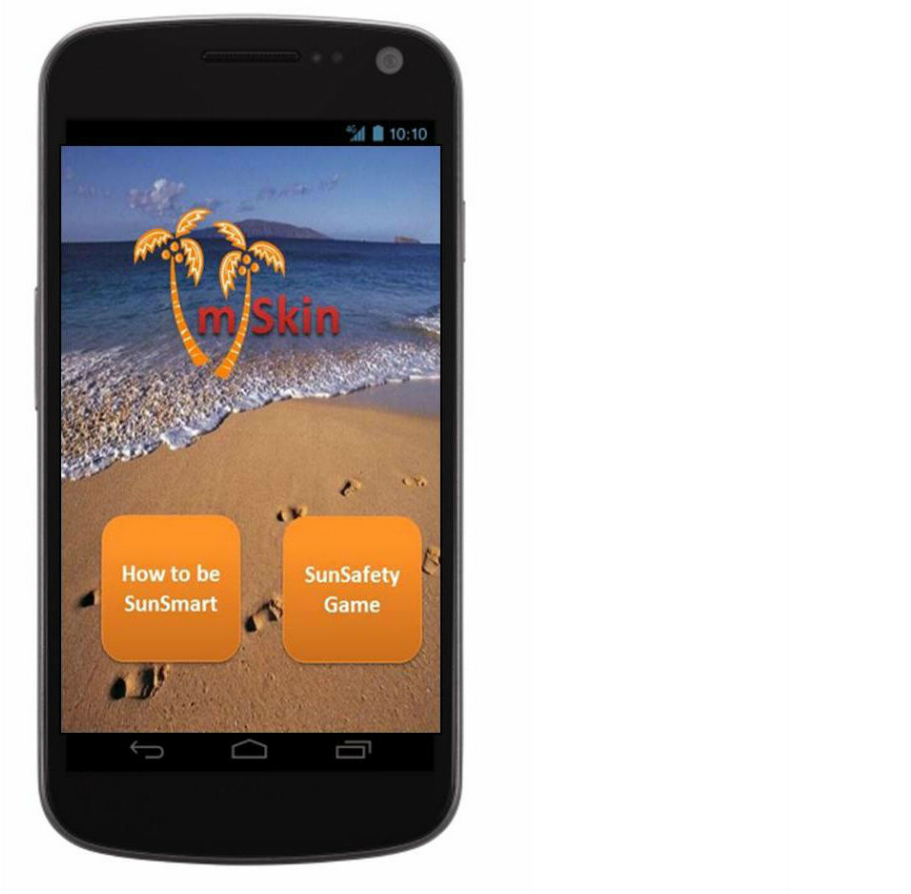
The aim of this stage was to obtain an exploratory evaluation of the intervention principles and resulting prototype. Individual interviews were used to obtain feedback and suggestions for improvement by giving the participants a key role in optimizing the intervention (co-design).

Eligible participants had to be over 18 years old with past experience of sunny holidays abroad. Included participants were assessed for inclusion criterion and were required to provide informed consent before participation. Interviews were conducted by a female researcher (AR) with experience in interviewing. Interviews lasted between 30-50 minutes and were audio-recorded and transcribed.

Participants were shown the interactive mock-up of the *mISkin* app (Figure 2), with a brief demonstration of the main

functionalities of the app. Participants were asked to interact with the mock-up and provide feedback, highlighting their satisfaction and dissatisfaction with the design, content, and format. Individuals were asked to provide suggestions for improvement (Multimedia Appendix 1: [Co-design individual interview topic guide]).

Figure 2. The mISkin main screen mock-up.



Analysis

All transcripts were imported into NVivo 10.0. Participants' feedback on the prototype was summarized into main suggestions, in order to refine the smartphone app before the feasibility pilot study.

Stage 4: Refinement of the mISkin App

Procedure

Based on the engagement and experience of the participants, a list of suggestions for improvement was compiled for discussion within the research team. In the participants' views, these suggestions would improve the acceptability and usability of the *mISkin* app. The way these were prioritized and implemented was based on whether their feedback indicated that a feature was potentially off-putting.

This stage was also informed by the key findings from a qualitative study with holidaymakers reported elsewhere [30].

Analysis

There were some discrepancies between the data gathered in this stage and the guiding principles produced by the research team in an earlier stage. The feedback provided by participants on the UV photographs was mixed (ie, both positive and negative reactions). However, visualizing UV photographs was an essential component of our intervention package, as previous studies had shown that these images might be effective in motivating people to improve sun-protection practices whilst on holiday [21]. In addition, findings from the qualitative study [30] suggested that respondents showed a desire to tan and attributed a high value to a tanned appearance during holidays. The conclusions also suggest that future public health messages should highlight the harmful effects of sunlight on appearance and demonstrate effective ways of performing sun-protection practices (eg, applying sunscreen properly).

Despite some users expressing negative reactions to the UV photographs (eg, fear or worry), all participants thought it was an important element to be included in the app. Consequently, UV photographs were retained in the *mISkin* app, but risk communication was improved in order to provide more health-related information before showing the UV pictures to the users.

Another discrepancy was the assumption about the potential disruptiveness of the Sun Alert service for users. The initial mock-up only assumed two prompts per day in order to avoid annoying users with alerts. However, feedback given by users was to make this feature customizable as some would have liked to receive more than two prompts per day.

Results

Stage 1: Identifying Active Ingredients, Behavior Change Theory, and Modes of Delivery Evidence

Findings

Table 1 details the list of included BCTs and presents the rationale. A systematic review of previously tested interventions to promote sun-protection provided pointers and evidence-based constraints for the design of this intervention, allowing for evidenced-based intervention development [21]. The pointers comprised effective BCTs and the need for any intervention targeting holidaymakers to be scalable and geographically flexible, delivered "on site" and not before holidays. The evidence-based constraints that had to be dealt with were as follows: (1) the lack of details on the development process of previous interventions, (2) the lack of mobile-phone interventions identified in the systematic review conducted, and 3) the lack of evidence available in the systematic review on the "how to" procedures for the intervention delivery.

The analysis of the active components provided useful information for intervention development [21]. We followed the recommendations of the systematic review to include BCTs that were consistently present in all interventions previously conducted in the field, by providing information on the consequences of performing sun-protection and on how to perform relevant sun-safety behaviors. The BCTs most strongly associated with effective interventions were also included in the app, namely (1) stimulate supportive social norms for sun-protection behaviors (eg, providing information about others' behavior and social norms), and (2) provide appearance-based information about skin photoaging, illustrated with UV photographs of skin damage. While the findings of the systematic review are informative, they are not considered to be definitive or sufficient to fully design a behavioral intervention and, therefore, other information sources were used to inform the development of all the components of the *mISkin* app, such as other systematic reviews and consultations with experts (eg, the need to include information on Vitamin D). Evidence on the most effective BCTs and associated theoretical mediators from other systematic reviews targeting behavior change [15,25,26,31,32] was also used to inform this stage.

This review [21] also found evidence for different modes of delivery. Interventions using written information and face-to-face communication were more effective than interventions using interactive sessions. Interactive activities were defined as demonstrations, games, and puzzles, used primarily with children to promote sun-protection. Delivering the intervention on site (eg, a holiday resort) was more effective than delivering pre-exposure.

Even though the systematic review did not provide specific evidence regarding smartphone use as a possible mode of delivery, other evidence suggested that this might be a novel, convenient, scalable, and feasible way of reaching the target population [15-18], given the widespread use of smartphones. Smartphones hold several advantages for behavioral medicine: (1) embedded location information (eg, GPS) can provide many important opportunities for hard to reach populations, (2) continuous uninterrupted data log, (3) capacity to support various multimedia apps, and (4) portability [29]. Holidaymakers are a volatile population present at different locations, which may make them difficult to reach. A scalable and geographically flexible smartphone intervention might be an effective way of reaching this population.

Stage 2: Consultations With Experts and Intervention Design

Findings

The intervention principles guided the design and development process of the app and added value to the experts' consultations. The key principles introduced based on expert advice were as follows: (1) development of an algorithm for sun-protection reminders (ie, using smartphone GPS data on indoor or outdoor locations), (2) vitamin D advice, and (3) introduction of gamification to deliver sun-protection information.

Any discrepancies between the different sources of data were solved based on the pre-specified intervention principles. For instance, the Vitamin D topic was added after consultation with experts in this area. However, this addition was congruent with our guiding principles in terms of providing health-related information within the app. Consultations with experts were essential to further develop and refine the intervention based on the iterative discussions with the core team members and wider consultations. One of the key challenges was the need to adapt to similar technical language when communicating within a multidisciplinary team.

The developed interactive mock-up and workflow of the *mISkin* app are presented in Figure 2 and Figure 3 respectively. Interactive mock-ups of the app were developed and used to test for ease-of-use, graphics appeal, and the general comprehension and acceptability of the distinct features of the *mISkin* app, using semi-structured interview methods.

The workflow was used as a design brief depicting the interaction process within the *mISkin* app that informed the development of a functional version of the intervention prototype by the app developers.

Table 1. Description of the *mISkin* app's main features, including behavior change techniques and rational for inclusion.

Feature	Description	Behavior change techniques[27]	Rational for inclusion (evidence-based and theory-based)
Skin sensitivity assessment with feedback	A set of 5 questions about skin reaction to the sun, based on previous literature (eg, [33,34]. After completion, participants receive feedback about their specific skin type and their reaction to the sun (eg, "You have skin type III. Sometimes burns, usually tans").	Provide information on consequences of behavior to the individual.	Understanding their personal risk of sunburn will help people shape outcome expectations, which in turn will impact goal setting. Evidence: A systematic review [21] outlines the importance of understanding the consequences of excessive sun-exposure. Theory: Social Cognitive Theory postulates that people tend to form outcome expectancies about the results of given actions [35]. In line with these outcome expectancies, people will engage in actions that are likely to produce positive outcomes and dismiss those that result in negative consequences [35].
NHS[a] Choices "How to apply sunscreen" Video[b]	The video provides information how to properly apply sunscreen, stating specific information about quantity, frequency, SPF, how to apply it before leaving the house, where to apply it, and guidance on sunscreen costs. The video also demonstrates how to apply sunscreen properly by showing a model doing it. The importance of other methods of sun-protection is also discussed in the video (ie, covering up and seeking shade). Special attention is devoted to children and the need for additional information about sun-protection. The risk of sunburn and skin cancer is also highlighted in the video. A snapshot from the NHS Choices video "How to be Sun Smart" was also included to foster social comparison on sun-protection habits.	Provide information on consequences of behavior in general, provide information on where and when to perform the behavior, provide instructions on how to perform the behavior, and demonstrate the behavior.	The video tackles all important instructions regarding sunscreen app, providing a complete display of the "how to do it" technique. The video also provides information about other methods of sun-protection and the consequences of excessive sun-exposure. Evidence: systematic review [21]. Theory: In the Social Cognitive Theory, instructions on how to engage in a specific behavior are essential to translate a goal into action, which will in turn foster self-efficacy and subsequent further behavior change [36].
UV[c] photographs	The app submenu "How to be Sun-Smart" also includes ultraviolet photographs of the face (male and female). Before displaying the pictures, a brief description is provided.	Provide information on consequences of behavior in general; fear appeals.	The inclusion of these types of photographs helps highlight the harmful effects of exposure to ultraviolet rays on people's appearance and, subsequently, promotes sun-protection habits. Evidence: Various systematic reviews [21,25,26]. The desire to have a tan is a central motive for sun exposure, as most people believe that a tan will improve personal appearance (eg, [37-39]. Research also shows that people find others more attractive when they have a tan [21,37,38]. Thus, interventions that highlight the negative effects of exposure to ultraviolet rays on one's appearance might lead to significant behavior change (eg, [21,37]. Theory: Social Cognitive Theory hypothesizes that people will engage in actions that are likely to produce positive outcomes based on outcome expectancies [35].

Feature	Description	Behavior change techniques[27]	Rational for inclusion (evidence-based and theory-based)
"Sun safety quiz"	This component engages holidaymakers in the "Sun Safety Quiz" by answering true or false to questions on general principles of sun-protection practices, information on positive consequences of sun-protection, tanning, vitamin D and UV Index. This is a gamification component, in which participants receive performance-based rewards (ie, positive feedback and final score message). Feedback provided also highlights others' use of sun-protection to facilitate social comparison.	Provide feedback on performance, provide information on consequences of behavior in general, provide information about others' approval, provide normative information about others' behavior, and facilitate social comparison.	A gamification feature was included in the quiz with feedback about performance and the provision of relevant information to facilitate social comparison. Evidence: Even though no conclusive evidence was unveiled by the completed systematic review [21], other systematic reviews have shown that self-regulatory strategies [31,40] and gamification [21,41,42] can be effective in changing other health behaviors. Theory: According to the Control Theory [43], feedback on performance provides external feedback on achievements and can lead to behavioral change. The Social Cognitive Theory hypothesizes that referential performance is induced by a process of social self-judgment, where social comparison is central. The provision of opportunities for social comparison is therefore an important strategy to influence referential performances and promote behavior change [35].
"Sun Alert service"	An algorithm was designed to define the main rules for interaction between the app and participants (Figure 3). This interaction is especially important to establish rules for delivering prompts for sun-protection. These prompts will occur between 10 AM and 4 PM and will depend on participant location (indoors or outdoors information based on smartphone GPS). Participants will receive approximately 2 prompts per day. In these prompts, a forecast of the levels of ultraviolet radiation will also be provided.	Prompt practice	Several studies showed that forgetfulness is a key barrier for sun-protection [44]. We believe that prompting will help individuals remember about sun-protection methods at least at two points in the day: (1) the start of the day, just before temperature starts increasing (ie, 10 AM), and (2) at midday when sun-protection (eg, seeking shade) is most needed. Evidence: Systematic reviews [15,21,31] and a previous trial on sunscreen use [19]. Theory: The Social Cognitive Theory envisages prompting as a key strategy for behavior change. Prompting enables individuals to experience mastery which promotes self-efficacy [45].
Diary record: ecological momentary assessment	Real-time data capture through the smartphone app is also used for assessment of sun-protection practices. This assessment will occur randomly between 11 AM and 3 PM, if the individual is outside (as detected by the GPS on the smartphone). Sun-protection practices will be represented by the use of symbols or pictures (please see Figure 5) and participants will only need to touch the screen to record the use of sun-protection.	Prompt self-monitoring	Self-report is prone to inaccuracies and biases in the reporting of behavior [46]. Smartphones can be an effective and feasible alternative to self-report for sun-protection assessment, especially because these devices can collect behavioral events in natural settings and produce time- and date- stamp events [47]. Evidence: Previous systematic reviews have shown the efficacy of this strategy in changing behavior [31,32,47,48]. Theory: Self-monitoring is a key strategy for behavior change for both the Control theory [43] and the Social Cognitive Theory [36]. Monitoring present behavior can lead to comparisons between actual behavior and standards and, subsequently, adjustments in performance in order to reach behavioral standards.

[a]NHS: National Health Service.

[b]Permission was granted by NHS Choices to be used in the mISkin application.

[c]UV: Ultraviolet.

Figure 3. The mISkin app workflow.

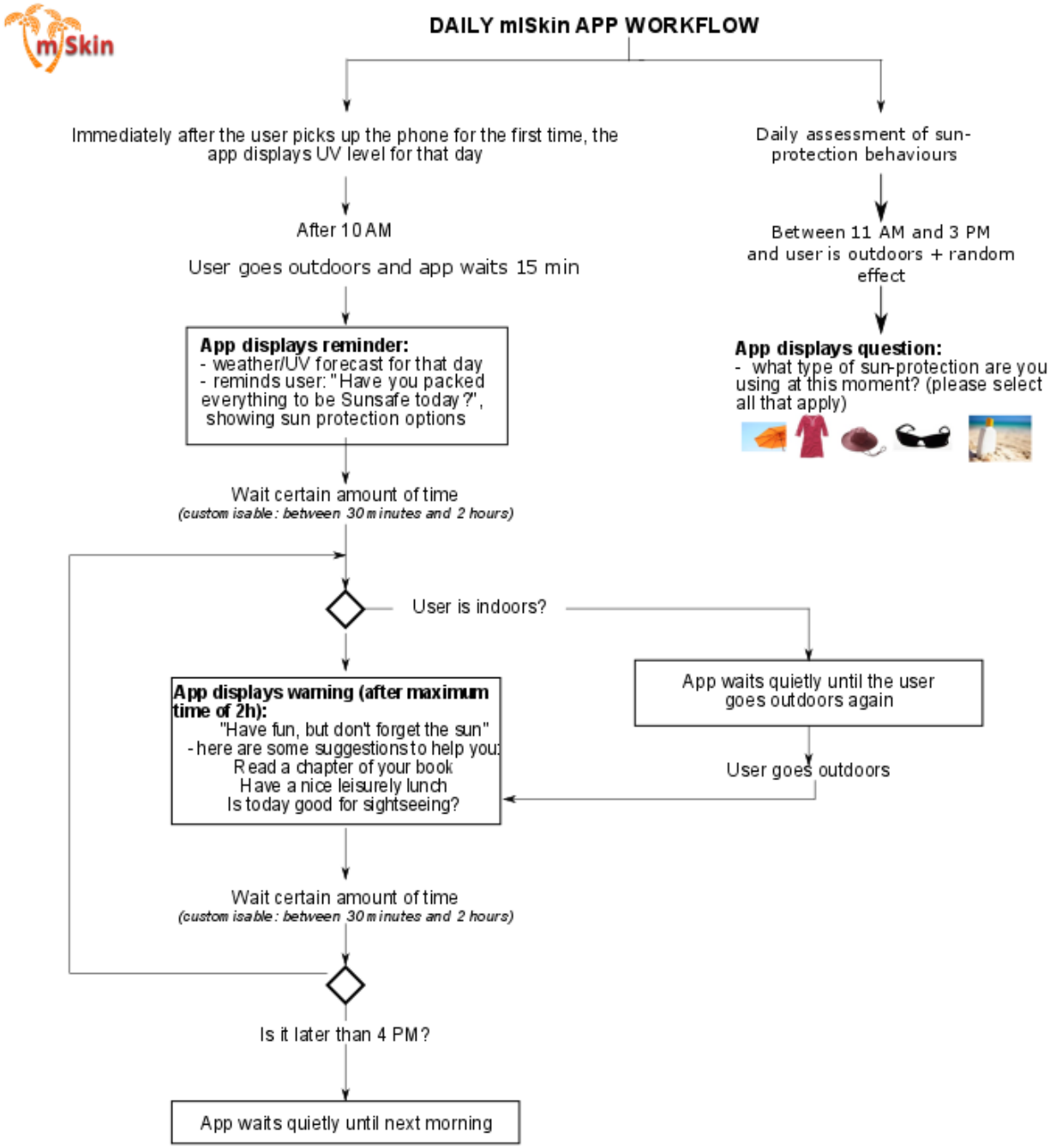


Figure 4. Main screen of the mISkin app.

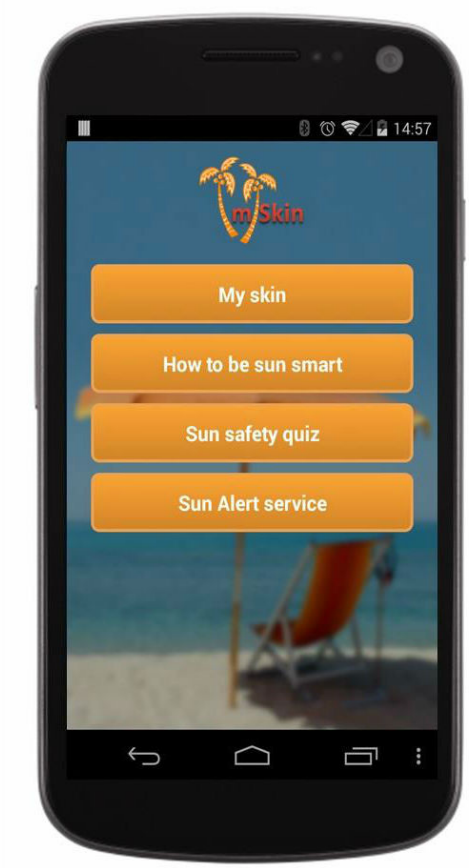
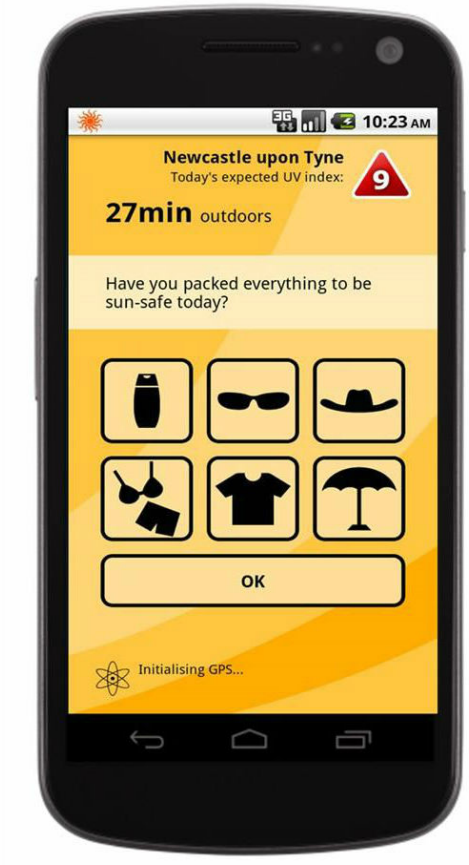


Figure 5. The Sun Alert service main screen.



Description of the mISkin App Prototype Mock-Up

The proposed smartphone intervention (*mISkin* app) was developed on the Android platform. The app entails a behavioral intervention using several BCTs to promote sun-protective behaviors amongst holidaymakers. Table 1 describes the main features of the *mISkin* app with explicit justification of inclusion based on evidence.

Stage 3: Evaluation of the mISkin App Prototype

Findings

Table 2 summarizes the feedback provided by participants on the specific features of the *mISkin* app and the suggested changes to improve ease-of-use, appeal, and usefulness.

Table 2. Feedback on the *mISkin* app provided by participants and changes introduced.

Intervention component	Category of suggested changes	Sample quotes	Changes implemented in the intervention
Skin assessment	Order of questions	"Information about specific skin types was quite useful." "Having the question about the skin reaction before the color of the skin in the skin assessment."	The question order about skin reaction was changed.
Videos	Video content	"It would be quite useful to see the clip again after seeing all the information in the little quiz or having the video after." "I like the practical advice about how much sunscreen to put on. I would say it would be more effective if it didn't leap straight into skin cancer and it started with choose a good sunscreen and then link to the consequences of not doing it." "I think it would be quite good to have a checklist at some point that we could look up."	A video menu was added to make navigation through different sections easier (eg, how to apply sunscreen and instructions for other sun-protection behaviors)
	Video length	"Instead of having a very long video having the different sections."	Different snapshots of the videos were added to the menus, reducing the information displayed. The video menu was organized so that skin cancer information is the last video displayed.
Sun safety quiz	Content	"In the quiz, instead of saying just true or false, say something like you're correct or that's wrong." "I like the quiz bit; you can do it once."	Explicit feedback on performance was added.
	Confusing statements in quiz questions	"Tricky question the one about sunburn doubles the risk of skin cancer."	The sentence was changed to "increased risk of melanoma."
Prompts	Content	"Like you say stay out of the sun between 10 and 4pm. Give some ideas how to do that. Like say have a nice long leisurely lunch sounds much better than you must stay in the shade between 10 and 4pm."	Some suggestions on how to seek shade between 10 AM and 4 PM were added to the reminders.
	Frequency	"I quite like it particularly the prompts. I would probably like to have a bit more, have the opportunity to remind me a bit further." "I like the idea of a sunscreen reminder app that I could set up to my preference."	A preference setting was added to the alert service, so that reminders are customizable (ie, 30 minutes to 2 hours).
UV[a] photographs	Reaction	"It's quite scary though, is it? I've seen a few of these before and it always makes you feel I should put more on." "It's a good idea to have it in and it's better than when that woman talking. Just put it a bit earlier in the app. it's the shock factor that would make you think: oh I don't want to look like this. So I suppose it should be in..." "It's quite scary; it might put me off the app. that the last thing I want to see on holiday."	UV photographs were moved to the video menu (participants visualization of these depends on their choice) and were placed as the last available option to be seen. A brief explanation about the meaning of the UV photographs was also added so that participants are aware of what it implies and know what to expect.

[a]UV: Ultraviolet.

Ease-of-Use of the mISkin App

Overall, the intervention was well-received by participants and described as appealing and interesting to use.

> *Having the information is good as I don't think people know. Also the reminders are good as on holidays sometimes you forget and it's good to be reminded.* [Female, 32 years old, with skin type III]

> *I like the tone about you're on holidays, here is how to be on holiday without "killing yourself," like the kind of how to enjoy your holiday.* [Male, 28 years old, with skin type IV]

Most users found that the app was useful and stated that they would use it on their holidays. There was a general satisfaction with the app.

> *I think I would do (use) and I think especially if you've got children as well, you know, I think that's really good. I mean my children are all grown up now but I do have a year old granddaughter so it's, I think it would be good because when you're a busy mum or grandparent and you sometimes forget to do things when there's a lot going on so...* [Female, 55 years old, with skin type II]

Users also mentioned the ease-of-use of the app and how the app is "intuitive to interact with" and provides information that is understandable.

> *Information needs to be there so that people know and can protect themselves. It was simple information and got the message over. I don't think it was boring, it was informative and that's something you need.* [Female, 55 years old, with skin type II]

Appeal of the Different Interfaces of the mISkin App

All participants provided positive feedback regarding the appearance of the *mISkin* app, stating that the background image, design, graphics, and color scheme were all appealing. "I quite like the design," said a female respondent aged 55 years, with skin type II.

Stage 4: Refinement of the mISkin App

Findings

After the amendments and refinements, the research team produced an optimized *mISkin* app reflecting user preferences. The active ingredients of the intervention were kept the same, with the main refinement being in terms of design to improve usability and acceptability. A final fully functional *mISkin* app was produced to be tested in a pilot randomized controlled trial (to be reported elsewhere).

The main elements of the *mISkin* app are providing general information about the consequences of unprotected sun-exposure, addressing appearance-related concerns, providing instructions for sun-protection, providing demonstration (modeling) on how to perform sun-protection behaviors, prompts for effective sun-protection when outside (via smartphone GPS), and feedback on exposure and protective behaviors. The app also includes a skin assessment questionnaire. Participants are prompted daily (a minimum of 2 times per day) by the app. Each day, participants are also prompted to respond, through the app, to brief questions about their sun-protection practices (ecological momentary assessment).

The *mISkin app* (Figures 4 and 5) has four main menus: (1) "My skin," (2) "How to be sun smart," (3) "Sun safety quiz," and (4) "Sun Alert service."

First, the " *My skin* " menu has a skin sensitivity questionnaire with general feedback on skin type. The BCTs used provide information on the consequences of unprotected sun-exposure for each individual according to skin type.

Second, the " *How to be sun smart* " menu contains videos on sun-protection recommendations: *"How to apply sunscreen*," *"Choosing a good sunscreen*," " *Other methods of sun-protection*," " *Preventing damage*," "*Protecting children*," " *Others' use of sunscreen*," and skin damage information depicted in combination with UV photographs. The BCTs used in the videos provide information on the consequences of behavior in general, provide information on where and when to perform the behaviors, provide instructions on how to perform the behaviors, and demonstrate the behaviors. The BCTs used in the UV photographs provide information on the consequences of behavior in general and on appearance-based fear appeals.

Third, the " *Sun safety quiz* " menu has a game with questions about sun-protection and tanning beliefs, with provision for immediate feedback that would give information on general recommendations for sun-protection. The BCTs used provide feedback on performance, provide information on the consequences of behaviors in general, provide information about others' approval, provide normative information about others' behavior, and facilitate social comparison.

Fourth, the " *Sun Alert service* " menu prompts about sun-protection a minimum of 2 times per day and with the option to customize these prompts in accordance with participants' wishes (eg, times and frequency). The BCT used was prompt practice.

Self-monitoring: This refers to the assessment of sun-protection practices between 11 AM and 3 PM if the person is outside (detected by the app) at least once a day and can be customized by participants. The BCT used was prompt self-monitoring of the behavior, as well as of the outcome of it (redness and burning).

UV levels are forecast with an indication of the most effective protection behavior. The BCT used was prompt practice.

Discussion

Principal Findings

This paper described a systematic and iterative approach to the development of the *mISkin* app aimed at promoting sun-protection during holidays. The sequential approach to development integrates different strands of evidence to inform the design of an evidence-based intervention. A systematic review on previously tested interventions to promote sun-protection provided cues and constraints for the design of this intervention. The development and design of the *mISkin*

app also incorporated other sources of information, such as other literature reviews and experts' knowledge and experience. The developed prototype of the *mISkin* app was evaluated by engaging potential holidaymakers in the refinement and further development of the *mISkin* app through usability (ease-of-use) and acceptability testing of an intervention prototype. All 17 participants were satisfied with the *mISkin* prototype and expressed willingness to use it. Feedback on the app was integrated in the refinement process to produce a final fully functional app before a formal test in a feasibility study. The feasibility and acceptability of the *mISkin* app has been formally tested in a pilot randomized controlled trial (Trial ID: ISRCTN3943558), which will be reported elsewhere.

Limitations

While the views of the 17 participants were coherent and data saturation was achieved, not all groups of potential users were similarly represented and it is possible that a more extensive engagement of potential users would lead to further improvements in acceptability and usability. The *mISkin* app was only developed for devices using the Android operating system, limiting the possibility of including users owning other smartphones (eg, iPhone and Blackberry). It is also important to highlight that the participants' views were based on only visualizing a prototype intervention aimed to be delivered during holidays. Views of using the app could change if participants were given the possibility of interacting with the *mISkin* app in a real scenario of holidays. It would have been useful to have a group of users that tried out the app on their own, followed by an interview about their experiences (ie process evaluation built into a pilot acceptability and feasibility study). This would provide further insight into how people perceived and used the app in their own time, which may be different from when a researcher is present [49]. The study did not explore what participants would want to see in an app for sun-protection during their holidays. Instead, they were shown the prototype of the *mISkin* app, potentially losing their general and a priori ideas about what should be in a sun-protection app.

Comparison With Other Studies

User-centered design is an approach that entails the involvement of potential users in the design process of a product (eg, intervention materials) by tackling their specific needs [22]. This process usually involves eliciting feedback from users by showing a prototype version of the intervention and implementing formative usability testing [22]. Other studies have used formative evaluation and shown similar findings on the potential of a smartphone intervention [24,50].

A key feature of the *mISkin* app is the Sun Alert Service and we were aware of the risk of participants becoming annoyed with receiving alerts or reminders within the *mISkin* app. As in similar studies, participants were keen to gain control over the settings for the Sun Alert service [24,50], in order to be able to customize the alerts (ie, quantity, frequency, and timings). Participants also raised concerns over the information about skin cancer and how this might impact the acceptability of the app and their willingness to use it. Other studies have identified similar challenges when communicating behavior change and health-related awareness [50]. The issue about avoiding provoking adverse emotional reactions becomes more prominent when discussing the UV photographs, as participants had mixed opinions about this feature. However, in the context of sun-protection, the evidence suggests that negative emotional reactions play an important role as predictors of sun protection [51].

Conclusions

This study summarizes the sequential and iterative process of developing the *mISkin* app, which was aimed at promoting sun-protection. Prototype testing provided useful information regarding users' views on and experiences from engaging with the *mISkin* app. Suggestions made by participants were incorporated in the refinement and development of a fully functional *mISkin* app. The optimized version of the app is ready for formal testing in a feasibility pilot study, to explore whether it is a feasible vehicle to deliver an intervention aimed at improving sun-protection amongst holidaymakers.

Acknowledgments

The work described in this paper was funded by a PhD fellowship from the Portuguese Science and Technology Foundation (FCT) (Reference: SFRH/BD/60392/2009). Angela M. Rodrigues and Falko F. Sniehotta were funded by Fuse, the Centre for Translational Research in Public Health, a UK Clinical Research Collaboration Public Health Research Centre of Excellence based on funding from the British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, Medical Research Council, and the National Institute for Health.

Conflicts of Interest

None declared.

Authors' Contributions

AR, FFS, MBM, PO, and VAS conceived the idea for the study together. AR collected the data, performed the analysis and drafted the manuscript. All the authors contributed to data interpretation and critically reviewed the manuscript.

Multimedia Appendix 1

Co-design interview topic guide.

[PDF File (Adobe PDF File), 29KB - resprot_v6i6e112_app1.pdf]

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Abbreviations

BCT: behavior change technique
NHS: National Health Service
UV: ultraviolet

Edited by G Eysenbach; submitted 20.12.16; peer-reviewed by M Bestek, L Morrison; comments to author 12.02.17; revised version received 07.04.17; accepted 02.05.17; published 12.06.17.

Please cite as:
Rodrigues AM, Sniehotta FF, Birch-Machin MA, Olivier P, Araújo-Soares V
Systematic and Iterative Development of a Smartphone App to Promote Sun-Protection Among Holidaymakers: Design of a Prototype and Results of Usability and Acceptability Testing
JMIR Res Protoc 2017;6(6):e112
URL: http://www.researchprotocols.org/2017/6/e112/
doi:10.2196/resprot.7172
PMID:28606892

Original Paper

Data Collection for Mental Health Studies Through Digital Platforms: Requirements and Design of a Prototype

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Abstract

Background: Mental and behavioral disorders are the main cause of disability worldwide. However, their diagnosis is challenging due to a lack of reliable biomarkers; current detection is based on structured clinical interviews which can be biased by the patient's recall ability, affective state, changing in temporal frames, etc. While digital platforms have been introduced as a possible solution to this complex problem, there is little evidence on the extent of usability and usefulness of these platforms. Therefore, more studies where digital data is collected in larger scales are needed to collect scientific evidence on the capacities of these platforms. Most of the existing platforms for digital psychiatry studies are designed as monolithic systems for a certain type of study; publications from these studies focus on their results, rather than the design features of the data collection platform. Inevitably, more tools and platforms will emerge in the near future to fulfill the need for digital data collection for psychiatry. Currently little knowledge is available from existing digital platforms for future data collection platforms to build upon.

Objective: The objective of this work was to identify the most important features for designing a digital platform for data collection for mental health studies, and to demonstrate a prototype platform that we built based on these design features.

Methods: We worked closely in a multidisciplinary collaboration with psychiatrists, software developers, and data scientists and identified the key features which could guarantee short-term and long-term stability and usefulness of the platform from the designing stage to data collection and analysis of collected data.

Results: The key design features that we identified were flexibility of access control, flexibility of data sources, and first-order privacy protection. We also designed the prototype platform Non-Intrusive Individual Monitoring Architecture (Niima), where we implemented these key design features. We described why each of these features are important for digital data collection for psychiatry, gave examples of projects where Niima was used or is going to be used in the future, and demonstrated how incorporating these design principles opens new possibilities for studies.

Conclusions: The new methods of digital psychiatry are still immature and need further research. The design features we suggested are a first step to design platforms which can adapt to the upcoming requirements of digital psychiatry.

(JMIR Res Protoc 2017;6(6):e110) doi:10.2196/resprot.6919

KEYWORDS

data collection framework; mental health; digital phenotyping; big data

Introduction

Mental and behavioral disorders are the main source of human disability worldwide [1]. Together with neurological disorders, they account for more than 10% of the global burden of disease, exceeding the load of both cardiovascular diseases and cancer [2,3]. In addition to high amounts of years lived with disability due to mental disorders, these illnesses are also one of the substantial causes of death worldwide [4,5].

Mental disorders are challenging to detect and diagnose, in part due to lack of reliable biomarkers [6], and as such, their treatment is a labor-intensive process. Psychiatric diagnoses are typically based on structured clinical interviews that rely on patients' conscious recall and ability to reflect on past events, thoughts, moods and behavior [7]. However, retrospective recall of variations in the patient's affective state is inaccurate, particularly if symptomatic variations take place within a temporal frame of hours or days [8,9]. This reduces the accuracy not only in diagnostic evaluations, but also in treatment responses. Besides symptoms, personal, behavioral, and social patterns are also important cues for understanding a patient's state. Thus, there is a genuine need for conclusive markers.

Because of the increase in use of modern technologies in recent decades, such technologies can collect vast amount of high-quality data on an individual's daily life and behavior, which are not affected by recall biases [10]. These technologies and the data they produce are promising both in psychiatric research and the clinical domain [11].

The use of technology in psychiatry dates back to early 90's [12], but recently some studies have used more modern digital platforms to actively and passively collect data from patients, to investigate markers, or to predict new episodes of disorders. Most of these studies focus on schizophrenia and bipolar disorder, such as MONARCA [13], CONBRIO [14], FOCUS [15], and Beiwe [16]. Moreover, most of them have shown promising primary results [16-19]. However, with the high rate of production of new tools, especially mobile phone apps designed to aid patients with mental disorders, the evidence behind the usefulness of these tools is still scant [11,20].

It is clear that more studies are needed to collect large amounts of digital data from patients in order to identify and validate the most useful types of data and to provide evidence for clinical use of digital technology in psychiatry. To date, most studies which collect digital data from patients have used monolithic systems designed specifically for that study. Consequently, the majority of the literature is focused on the results and less attention has been paid to features of the data collection platforms. Inevitably new digital data platforms will emerge in the near future that address the need for large-scale data collection for psychiatric research. Therefore, it is important that research protocols and features of these platforms be shared among researchers in this field, in addition to the results that these platforms produce.

Working in a multidisciplinary group composed of psychiatrists, system designers, and data scientists, we identified the following main features we believe emerging data collection systems for psychiatric research must have: (1) flexibility of access control, to have more simultaneous interdependent studies of the same participants and more control over data mixing; (2) flexibility of data sources, to provide an automatic and systemic linking of diverse sources at minimal upfront cost; and (3) first-order privacy protection, to guarantee the data is being used as the participants consent. The first and second features will give researchers in the field of psychiatry the possibility to easily design studies (even multiple parallel studies) and identify the devices and digital sensors that are most helpful and data from them can be translated to clinically relevant measures. The first feature will also provide data scientists maximum flexibility when analyzing the data, without being restricted by the initial design. The third feature guarantees privacy for patients and will also help to protect researchers against accidental breaches of privacy regulations. Most of these features can be generalized to any digital data collection study; however, because there have not been many studies in the field of digital psychiatry, flexibility both in terms of access control and data sources becomes ever so important. In addition, extra sensitivity of patients' data calls for more severe measures of privacy. While these features can always be implemented after the fact, top-level consideration makes for the most efficient and secure method of working.

In addition to the identified features, we also presented the Non-Intrusive Individual Monitoring Architecture (Niima) platform designed to meet these 3 key points, allowing fine-grained support for multiple, longitudinal, overlapping studies. Niima integrates various existing data sources powerfully and with flexibility to achieve new data mixing approaches while keeping privacy among different overlapping studies. Niima can be used for randomized studies with patients with mental disorders and healthy controls, or even for studies with general population cohorts where studying the behavior and activity of participants is desired. Data from multiple sources coming from each participant is securely linked to their account on the Niima platform and can later be anonymously accessed by the researchers. Niima ensures the privacy in each part of the data collection, transfer, and analysis processes. Using Niima, researchers can add new sensors to the study during its course without interfering with the data collection already happening or even run multiple studies with overlapping or independent sets of participants simultaneously. Niima also envisions "independent users" who get access to their own data. These users are pilot testers of each study setup that provide feedback to researchers and help optimize the setup.

Methods

In this section the background for each of the key design principles and how they could be implemented are described.

Flexibility of Access Control

Motivation

Research has advanced to the point where simple studies with human participants are routine. In these studies, data are collected and analyzed to answer the specific project questions. In the context of mental health, the longer people can be observed the better able we are to find clinically relevant variables. However, because using big data in psychiatry is relatively new, there is still little known about what these clinically relevant variables are and how they might be different from one disorder to another. It is now required that we " scale out": this does not mean to scale to more data or more participants as this type of scalability is relatively straightforward with modern big data tools. Rather, we mean scalability to longer time periods, more simultaneous data sources, more simultaneous interdependent studies of the same

people, more remixing of data, etc. This will give researchers the possibility to validate their findings and apply them in the clinical domain. As an example, one might want to conduct repeated data collection experiments with the same cohort of mental-health patients, say, initially using phone tracking apps, so that additional sources of data—bed sensors or activity trackers—are incorporated as soon as their value to the researchers becomes apparent.

In order to achieve its goals, a data collection system must adopt a good model of users, data sources, studies, and the flow of data between these. If it does not, it may be limited to the "one pot" model of data collection, without the ability to manage the process and data flows. The data model described here allows us to achieve our other goals of flexibility of data sources and privacy easily.

Implementation

Access Control

Niima implements 3 types of users: administrators, researchers, and users (participants) (Figure 1). Administrators have the ability to set up the study parameters, but do not access raw data for research purposes. The administrators may be system-wide, or per-study, depending on the level of independent supervision needed. The managers (a type of researcher) set up the study and have access to the creation of users and devices. Managers and other researchers only have access to data after it has been processed for privacy. The participants or users are the people who provide data. This 3-tier system provides the basis of our privacy system. While this seems obvious, it is important to properly plan and design things in advance. Once a proper role system exists, we can add rules which further improve data protection by limiting access to different people. For example, one could separate those who interact with the participants from those who access the data, providing further privacy to participants. If a proper role system does not exist, then implementing access control becomes difficult and error-prone.

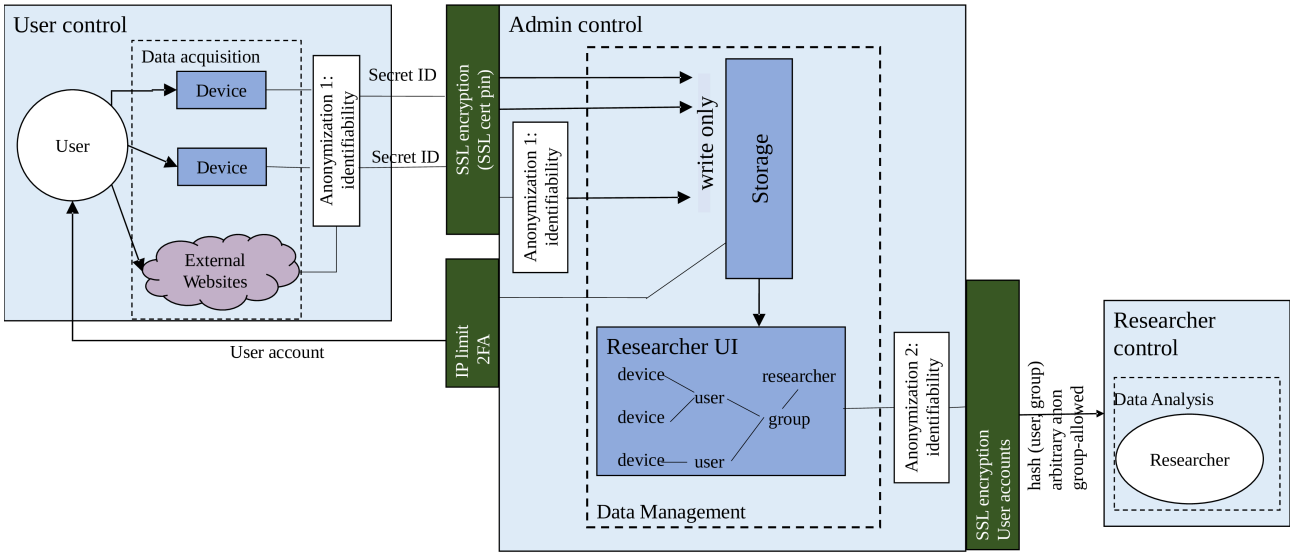
With Niima, across different studies, users will preserve the same user account, while their role might change from one study to another. In addition, they can be simultaneously part of different studies while having a different role in each. It is even possible for one user to have more than one role within a single study (Table 1).

Table 1. The role system structure of Niima.

Actions	Role				
	Administrator	Manager	Researcher	Participant	Independent user
Has user account	Yes	Yes	Yes	Yes	Yes
Configures study	Yes	No	No	No	No
Adds/removes users within study	No	Yes	No	No	No
Views raw data	No	No	No	No	Yes (only own)
Enrolls participants and configures their devices	No	Yes	No	No	No
Has access to data after converters	No	No	Yes	No	Yes
Gets access to own user account	Yes	Yes	Yes	No	Yes

An individual's data is stored connected to a user account on the server. A user account is separate from any particular study. Users may be a part of none, one, or more studies. A user not associated with any study is defined as an "independent user" and is discussed below.

Figure 1. Outline of the Niima privacy model. The strict separation of roles user, researcher, and administrator provides the basis of all work. Data anonymization can be performed both before data is received and again before it is provided to researchers. The study-user-device model provides for fine-grained access control.



Study Model

Each study contains various metadata, which provides fine-grained access control. First, it contains participants and researchers. Data from participants is made available to the researchers. A start and end date defines the available data range, which is important so that more limited data access may exist even while data is being collected longitudinally. The study also defines "converters," which specifies what data is available to the researcher. Because the converters are defined per-study, each study's researchers will get only the data necessary for their purposes, even if data from participants is being collected for other studies.

Each participant may have multiple devices of any type, so, for example, if a user has 2 phones, data can be collected from both of them. A "device" only consists of a device identification (ID) and a place to store data under that ID. This is what allows us to easily scale the data collection task to any number of data sources per person.

Independent users (not part of any study) can view all of their own data, including the raw data. One reason creating independent users was that in contrast to classical clinical studies, studies which use digital platforms require pilot participants and testers. Having independent users makes it possible for researchers to test the system with these users (who preferably have technical knowledge or study-specific knowledge) and can give good feedback about the study design and setup.

Transparency—the right to inspect one's own data—is an important principle of personal data processing [21]. Our system has the possibility of transparency by allowing user accounts for participants, which can be used to inspect their own data like independent users can. However, where this is not desired (eg, clinical studies), it is not required. Because of this design, our system is equally usable as a public service. This can be used to attract volunteers as part of studies. Thinking about both the within-studies and independent use cases together forces us to design a system with a focus on individual rights, making privacy natural.

In our design thus far, independent users are given full access to their own raw data in addition to converters which make the data easy to use. Studies are limited in the converters they provide, to only allow required data through.

Separating users and studies and raw/processed data allows new possibilities and stronger privacy-preserving properties (see below). First, converters allow a much more fine-grained approach to privacy protection. Second, this is set up as a third-party anonymization service, which mediates between participants and researchers. With this system, a third party can provide privacy supervision and can help to ensure ethical supervision is being fulfilled. It can also allow longitudinal data collection with various overlapping short-term studies and even a safe way to collect more data than at first deems necessary. Finally, the introduction of independent users allows for a more participatory model of science, which is especially important when dealing with personal data.

Flexibility of Data Sources

Motivation

To find clinically relevant variables, we should not only look at different data coming from various sources in a certain device (eg different data streams produced by mobile phones), but also at other wearable and consumer devices that have become ubiquitous and can provide rich behavioral data (ie, activity trackers, ballistocardiogaphic bed sensors, and other types of devices) that are available to consumers [22]. It is important that data from these devices be studied and validated. Given the combination of many possible data sources and lack of certainty of the most useful and clinically relevant data, any data collection system must be flexible as to the data it collects. Another reason why it is important to have the possibility of collecting data from multiple devices for the same individual

at the same time is that mental disorders and chronic physical illness often appear as comorbid conditions [23]. As such, it would be too simplistic to treat comorbid conditions separately and to follow their trajectories individually [24]. Therefore, there is a need for changing the way psychiatric care is delivered that addresses this complexity [23]. There are many frameworks and mobile phone apps that help with monitoring chronic physical illnesses [25,26]. Having the possibility of collecting data on physical and mental comorbidities at the same time in future studies, would provide valuable insights for better understanding these comorbidities and providing better solutions for them.

Implementation

To be a viable research tool, a system must be able to quickly adapt to new sources of data. Our system is designed from the ground up to integrate many sources of data. The goal is to be able to integrate any new data source with minimal upfront cost. As new data sources are identified, we can quickly integrate them because of the flexibility of our data model.

Our platform adopts the "lambda architecture" of data systems [27]. In this architecture, all incoming data is saved raw and not modified. Data interpretation and processing is performed as a second stage, which can be repeated and improved as needed with no risk of data loss. Currently, real-time access to data is not a priority of Niima, but should such access be needed, a third stage can store the processed data in secondary databases suitable for real-time querying and operations.

When data arrives in lambda architecture, it is stored raw (usually the raw text is received) and represented in whatever the original format was. This lowest common denominator format can work and is efficient enough for any device with modern storage and transparent compression. This means that data can be inserted in an efficient write-only operation, which also improves security. The flexibility and simplicity, and thus reliability, of this system more than makes up for any inefficiencies. We can easily accept data from any type of device, even devices with very limited programmability. Data is identified by a secret token when it is received, which is directly used to store the data. Data storage is stored only indexed by (device ID, timestamp), which allows us to use modern databases that scale to huge amounts of data.

The bases of the extraction stage are converters that convert raw data into structured, table-based formats. For example, a mobile phone device could have a converter that translates the raw text data about communication activities to call records, rehashing numbers and removing self-calls. Another example is converting detailed Global Positioning System (GPS) location data to quantities such as the average amount of movement per hour, in order to better preserve privacy. Each device type per study can have different converters ensuring that the data provided is specific and minimal.

One important benefit of this system is that the interpretation of the data is delayed to the conversion phase. The marginal cost of adding a device is very small; all that is needed is some interface to receive data and store it raw. All processing can be delayed until the relevant contents of the data are identified. This is especially important from a privacy perspective such that privacy and anonymization decisions do not have to be made immediately, but can be made (1) after the exact data needs are identified, (2) per-study (data minimization), (3) after unforeseen privacy risks are handled, and (4) in a fashion that can be minimal at first and improved over time.

This system also provides a decoupling between data source and usage. In a large study, data may come from devices that are not under the researcher's direct control. This may happen if, for example, our data is collected from an external service. It could also happen if a study lasts a long time and data sources need to be updated. It is easier to maintain a flexible data model than manage migrations. When all data is stored raw, it means that all but the largest of changes have no impact on receiving data. By versioning or simply examining the data received, the second-stage converters can decide the proper way to process it at some later time. This greatly simplifies the long-term maintenance of studies and allows us to maintain higher quality and more adaptable data collection for a longer time with fewer resources.

To demonstrate this system, we integrated a wide variety of data sources into our prototype system: 3 Android and 1 iOS app [28-30], an Internet of Things (IoT) device [22], server-side surveys, manual upload, actigraphs, and social media. The mobile phone apps send data using various application programming interfaces (APIs), and raw data is stored as the raw Javascript Object Notation (JSON). The IoT device is a Murata bed sensor [22] that also sends data via a Web API, but our server's endpoint must examine the data to determine the proper device ID. We have implemented server-side surveys, where participants can be asked questions and data is saved in JSON. For social media, our server interfaces using the public APIs. Finally, our system can be used for any other data. For example, we integrated Phillips Actiwatches (actigraphy devices). These were completely non-networked devices. Data was extracted from them with their existing software and then uploads were done manually, specifying only the proper device ID to link data with the user's profile. From that point, our system of converters and privacy tools took over.

With this system, we can effortlessly collect and merge data from almost any device. This forms the core of a vision where data may freely flow between different apps and platforms, as opposed to just from one data source to its intended collection server. The major lessons for developers are (1) separate data collection from data use (upload) via a simple API expecting that others will use it in other contexts, and (2) provide a method to specify the upload server address.

Privacy Protection

Motivation

Personal privacy is a critical part of research. It is especially important in health-related fields, where ethics and law are strict in their standards. Confidentiality is the cornerstone of all psychiatric patient evaluation or treatment. However, many existing data collection frameworks adopt a limited privacy model. These studies generally collect data with a "one pot" model: data is collected and goes straight to researchers,

stripping of direct identifiers. However, privacy is much more than this, it includes purpose limitation, fine-grained access control, tailoring anonymization to the intended purpose, etc [31]. While there are an almost unlimited number of things that could be said about privacy, there are a few important lessons. Some basic principles of ethical data access include (1) consent, meaning a person must approve the way data is used; (2) a participant should have access to their own data for examination; and (3) data minimization [32-34]. The basic solution to privacy in a scientific context is anonymization, the idea that while data may be shared, actual identities are not known and are not to be discoverable.

Unfortunately, this does not provide an actual solution, because instead of some specific criteria, this requires a lack of possibility of identification, which cannot be easily proven for our multidimensional and long-term data. Techniques such as k-anonymity and l-diversity can provide guidance about making data anonymous; however, because our type of longitudinal data is highly multidimensional these techniques do not apply [35,36]. With detailed, multifaceted data on people, it is nearly impossible to prove that a true anonymization has been done without destroying some useful aspect of the data. Thus, our architecture is designed around the principle of defense in depth. First, we do not collect direct identifiers at all, even as raw data. Arguably, this could make our data anonymous according to some interpretations. Second, when data is extracted, it is further anonymized, for example, by rehashing or aggregation. Third, each study can have its own separate anonymization based on a secret seed. This prevents linking data between different studies. Finally, researchers must agree to data protection by an agreement, including conditions of not identifying people. The combination of the above factors can be enough to satisfy the standard of “not reasonably likely” that a person could be identified, which is the most common standard. However, since there is no universal standard, all we can do is provide the tools and allow people to use them as needed.

Implementation

Identification Versus Linkability

It is important to note the difference between identities and linkability. Privacy risks appear when data can be linked to specified real persons. It reasons that in order to preserve privacy, we must eliminate the ability to link different data together. Removing direct identifiers is the most obvious way of preventing linkability to real persons. However, linking de-identified data to other de-identified data is also a risk, because once more is known it becomes easier to re-identify. With our more flexible data model, we have the possibility for multiple studies with access to different data from the same people. Our system provides tools to remove these possible links as well.

Converters

Converters are the basis of our privacy strategy. Each converter applies arbitrary transformation to the data before it is presented to the user. This gives us the ultimate flexibility of managing privacy. Converters do not only directly translate data, but can provide higher level operations such as aggregation. Further, since converters operate right before data is extracted, privacy can be continually improved. It is also possible to begin by releasing the minimal amount of data, and then incrementally release more as it becomes necessary or safe.

Hashing

Hashing of identifiers is the anonymization strategy. A one-way hash is a function which, given some data, produces a new meaningless identifier that is a function of that data [37]. These functions have mathematical properties such that the input cannot be derived from the output, which is useful for anonymizing identifiers such as phone numbers while still being able to connect identical events. While it is impossible to derive the input from the output, when there are a limited number of possible inputs, it is possible to test all inputs to determine the output, especially because these functions are designed to be fast. Purposefully slow hashing methods, such as those designed for password hashes, are too slow to apply in bulk and still are designed to allow one to verify a known input. Thus, we hash identifiers on the server using a secret salt, hash(salt+data) [38]. If the salt is long and secret, this allows for both speed and complete security. This is also done as a 2-stage process: first data are normally hashed on devices and a second round is done on the server with the secret salt. This is because a secret salt cannot be transferred to devices. This naturally integrates into the Niima architecture. Further, each study can use a different secret salt, so that the data for each study cannot be linked. Finally, in order to perform a final, absolute, and irreversible anonymization, the data can be exported with a one-time salt that is not stored anywhere.

Timestamp Anonymization

A similar process can be used for timestamps. In our data, even a single timestamp can prove to be identifiable. If a person knows that a user performed some action at a certain time (such as making a phone call), then regardless of any other anonymization, if that timestamp is unique in the data, the person can be identified. For larger amounts of data, even knowing times of a small number of events can fingerprint a specific user. Our system passes all timestamps through an arbitrary function, which can be used to apply a fuzzing to adjust timestamps. The exact function and amount of shifting must be decided based on what is necessary for research and anonymization.

Institutional Control

Hashing and timestamp fuzzing are only some examples of the types of privacy-preserving transformations made possible by the Niima architecture. Our structure is that of a third-party anonymization service. There is a strict separation of roles between the server administrators (who have technical control of the server) and researchers, and these levels balance between research flexibility and privacy. It is the administrators’ basic responsibility to manage the research consent between participants and researchers and to guide the researchers so that privacy is protected. In the upcoming European General Data Protection Regulation, there is an emphasis placed on privacy by design as well as institutional control [21]. The structure of our system provides a good basis for satisfying both of these criteria.

Results

In this section, use cases made possible by our work are discussed. As these are not classic studies, they require a very refined model of users and privacy. In the first, a student course was organized, primarily designed for pedagogical purposes. The flexibility of the system allowed the students to have full control over their own data and to adapt as the students proceed. In the second, we use the flexibility of our system to pilot a project.

Student Project

Collecting data from people is not just useful for scientific studies, but can be useful for pedagogical purposes as well. Working with students also provides an extremely rigorous test of privacy procedures, since students have a right to study without their data being required to be shared. We hosted a course where we provided the basic tools for data collection (Niima) and the students had freedom to choose the data sources and research questions they were interested in. As part of the course, students considered and solved privacy issues related to each of the data streams. Because this was a student project, we could not simply adopt the "one-pot" model of collecting all data and distributing it to everyone.

In the course, the students first collected their own data and independently analyzed it. Our framework's independent user accounts naturally facilitated this. After a period of considering their own data, the students planed research problems which used everyone's data. They considered privacy issues and decided what data could be shared, and most importantly, how anonymization could be performed. Their anonymization procedures were implemented into converters for their data sharing groups. In order to protect study rights, data sharing was voluntary, and to ensure there was no possible effect on grading, even instructors did not know who had opted into sharing data. This was handled by anonymous opt-in on the server. Thus, during and after the project, no instructor could even know which students opted for sharing; the only way to guarantee that there was no unconscious bias.

The students used a wide variety of data sources, including mobile phone apps (Purple Robot) [28], surveys, and the Murata Bed Sensor Node [22]. We could quickly adapt to the interests of the students. Partway through the course, some Philips Actiwatch II sensors became available and students decided to augment the data with this. Because of our design, adding these devices was trivial, even though they were non-networked and managed by legacy software. We added a new server device class for the Actiwatches, and students added it to their user accounts. Students provided only the device ID and this was used to register devices so that the instructors did not need to manage or ever record the subject identities themselves. The output data files were uploaded to the server so that students could examine them. After this, the relevant data was identified, converters were written, and the data was made available via a study.

Our system also allowed for incremental sharing. As we stated above, students always anonymously opted in to data sharing by joining a new study. By the end of the course, students were enrolled in different studies, each of which was for sharing a certain type of data. This provided granularity and specificity of purpose. Initially, only certain safe data was shared for a limited purpose of this course. Later on, students could anonymously opt in to sharing data for other purposes, such as donation for follow-up research or even sharing as open data.

The course was a vital pedagogical tool in these students' data science training. Real-world data and real-world problems in collecting the data are different from what is typically experienced in class. Unlike in structured courses, students experienced the difficulties in data wrangling and cleaning, which is a skill that can only be learned by doing. The Niima architecture was necessary because of the complex nature of the subject-researcher relationship and the fast-moving development of the project. The lessons and tools here also provided valuable lessons for prototyping other studies.

For us, this student project showed how data processing and access could be controlled with our system. Access for the data could be limited for each user type which made preserving privacy possible. Each data source required separate converters for anonymization and preprocessing. After setting up the converters, providing anonymized data and fine-grained access was easy.

Preparing for a Future Study

We will start using our tools in studies at the Department of Psychiatry of the Helsinki University Central Hospital. In preparation for this project, extensive testing is needed. We would like to get as many testers as possible; however, these testers also need privacy while still closely interacting with the developers. Moreover, because of the clinical implication of the data, privacy is an especially large concern. We divide the researchers into 2 categories: those who interact with participants (managers) and those who have access to the data. This access control was natural given Niima's design principles. This allows us to tell testers that their privacy is maintained; there is not one single person who can have access to both the identities of the participants and the data about them.

The data will be collected for 1 year uninterruptedly with different devices (mobile app, actigraphy, sleep sensor, experience sampling methods/ecological momentary assessment-(ESM/EMA-) based questionnaires, etc) at different moments in the research. The overlap of devices and change over time are easy to set up in Niima because of its scalability over time, participants, and data mixing. Moreover, Niima allows the grouping of different data sources of individual participants because of its flexibility of data sources, so even if the study requires a second change over its course, it will be possible to achieve and reconfigure easily.

Discussion

Principal Findings

It is important to distinguish between biomarkers used as (1) diagnostic tests, and (2) their use as indicators of illness state variations [39]. Our first goal when collecting data from patients with mental disorders should be the latter, because before being

able to benefit from them in practice, we need to answer the following crucial questions: (1) to what extent do parameters extracted from passive data covary with clinical states, and (2) how good of an indicator of clinical state can digital tools get? There are some studies that have tried to investigate this with respect to depressive symptoms by collecting data from a general population cohort and have provided a first proof-of-concept [40-42]. However, there is need for clinical trials with enough statistical power to maximize the chance of finding new biomarkers from the data. Even for bipolar disorder there are relatively more studies that have collected and analyzed passive data from patients [43]. More data from different populations are required so that in addition to new findings, previous results of past studies can be validated. In addition, there is a need for developing new methods for learning from such data [44]. These methods can be developed only if we have good data collection tools which can be widely used and if we can guarantee that experts from psychiatry work together with data scientists. Upon developing and validating such methods, if they prove to provide a better understanding of mental disorders, the newly found biomarkers can be used as diagnostic tests. However, real-world performance of a diagnostic test depends on prevalence of illness, thus, utility of any diagnostic tool is context dependent. Clinical trials should be performed as the ultimate utility test, in which patients' outcomes should be shown to be better using these methods.

Here, we presented features we believe are important for the design of a data collection platform for mental health studies and described a data architecture which allows more and better data to be collected. First, we outlined a model of users and studies that allows for a more sophisticated and flexible process from the perspective of the user. With this, it is natural to be able to run longer and more detailed studies. Second, our method of processing data allows much more flexibility of data sources and new data sources can be added with trivial cost. Combined with the first point, we no longer conceptualize research in terms of studies, but research in terms of people who are thoroughly quantified, where data flows in from sources and out to different users. In order to make this feasible, a model of privacy better than "remove identifiers" is needed. This model is both the third point and an outcome of the first two.

To demonstrate the power of this system, we implemented an initial prototype, Niima, which implemented the principles described above. By using this platform, we were able to engage in studies with more rigorous demands on privacy and flexibility than are possible using existing systems.

In the future, Niima can be used for different types of studies, and while studies with patients with different mental disorders has been one of the main use cases of the framework, it can be used in any kind of study requiring multi-sensor and/or multi-device data collection from human participants. Designing a platform for the original use case (patients with mental disorders) is perhaps the most challenging case of all types of data collection studies with human participants. By designing a system that accommodates the needs of one of the most difficult cases, the system can even more easily be used for behavioral studies for general population cohorts.

Conclusion

While we hope that technology quickly adapts to the needs of science that is not always the case. In many cases, the limits of technology set the limits of research. The models we propose do not so much represent a revolution in either science or technology independently, but represent new ways of using technology for science. Adopting these models, however, will not be instantaneous. In particular, proper methods will provide an agility for research which does not match the demands of pre-approval for human participant experiments. However, the models we propose are a definite improvement in the protections of the rights of participants, and we can hope the ability of better technology can eventually influence research ethics.

Acknowledgments

JS and TA acknowledge support from the Academy of Finland, project DigiDay (No 297195). KK and RD acknowledge support from the European Commission, projects IBSEN (No 662725) and SoBigData (No 654024). We acknowledge computational resources provided by the Aalto University Science-IT project and the Department of Computer Science. TA thanks Dr John Torous for many helpful discussions. TA is also grateful for the support of EIT Digital doctoral school.

Conflicts of Interest

None declared.

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Abbreviations

API: application programming interface
ID: identification
IoT: Internet of Things
JSON: Javascript Object Notation
Niima: Non-Intrusive Individual Monitoring Architecture

Edited by G Eysenbach; submitted 30.10.16; peer-reviewed by T Kowatsch, A Doryab, S Chen, J Torous; comments to author 28.11.16; revised version received 13.02.17; accepted 02.04.17; published 09.06.17.

Please cite as:
Aledavood T, Triana Hoyos AM, Alakörkkö T, Kaski K, Saramäki J, Isometsä E, Darst RK
Data Collection for Mental Health Studies Through Digital Platforms: Requirements and Design of a Prototype
JMIR Res Protoc 2017;6(6):e110
URL: http://www.researchprotocols.org/2017/6/e110/
doi:10.2196/resprot.6919
PMID:28600276

Original Paper

Development of a Web-Based Intervention for Addressing Distress in Caregivers of Patients Receiving Stem Cell Transplants: Formative Evaluation With Qualitative Interviews and Focus Groups

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Related Article:

This is a corrected version. See correction statement: http://www.researchprotocols.org/2017/8/e130

Abstract

Background: Caregivers of cancer patients experience significant burden and distress including depression and anxiety. We previously demonstrated the efficacy of an eight session, in-person, one-on-one stress management intervention to reduce distress in caregivers of patients receiving allogeneic hematopoietic stem cell transplants (allo-HSCT).

Objective: The objective of this study was to adapt and enhance the in-person caregiver stress management intervention to a mobilized website (eg, tablet, smartphone, or computer-based) for self-delivery in order to enhance dissemination to caregiver populations most in need.

Methods: We used an established approach for development of a mhealth intervention, completing the first two research and evaluation steps: Step One: Formative Research (eg, expert and stakeholder review from patients, caregivers, and palliative care experts) and Step Two: Pretesting (eg, Focus Groups and Individual Interviews with caregivers of patients with autologous HSCT (auto-HSCT). Step one included feedback elicited for a mock-up version of Pep-Pal session one from caregiver, patients and clinician stakeholders from a multidisciplinary palliative care team (N=9 caregivers and patient stakeholders and N=20 palliative care experts). Step two included two focus groups (N=6 caregivers) and individual interviews (N=9 caregivers) regarding Pep-Pal's look and feel, content, acceptability, and potential usability/feasibility. Focus groups and individual interviews were audio-recorded. In addition, individual interviews were transcribed, and applied thematic analysis was conducted in order to gain an in-depth understanding to inform the development and refinement of the mobilized caregiver stress management intervention, Pep-Pal (PsychoEducation and skills for Patient caregivers).

Results: Overall, results were favorable. Pep-Pal was deemed acceptable for caregivers of patients receiving an auto-HSCT. The refined Pep-Pal program consisted of 9 sessions (Introduction to Stress, Stress and the Mind Body Connection, How Thoughts Can Lead to Stress, Coping with Stress, Strategies for Maintaining Energy and Stamina, Coping with Uncertainty, Managing

Changing Relationships and Communicating Needs, Getting the Support You Need, and Improving Intimacy) delivered via video instruction through a mobilized website.

Conclusions: Feedback from stakeholder groups, focus groups, and individual interviews provided valuable feedback in key areas that was integrated into the development of Pep-Pal with the goal of enhancing dissemination, engagement, acceptability, and usability.

(JMIR Res Protoc 2017;6(6):e120) doi:10.2196/resprot.7075

KEYWORDS

cancer; caregivers; distress; anxiety; depression; stem cell transplant

Introduction

Background

According to the 2015 National Alliance for Caregiving and the American Association of Retired Persons Public Policy Institute, there are "43.5 million adults in the United States that have provided unpaid care to an adult or child in the prior 12 months" [1]. Estimates from 2013 suggest that unpaid caregivers provide upward of $470 billion in care to their family members [2]. Additionally, missing work due to caregiving responsibilities leads to an estimated $25 billion in lost productivity [2]. While the impact of caregiving on the economy is significant, the emotional impact on the caregiver in terms of depression, anxiety, and distress is also substantial [2].

Caregivers of patients receiving hematopoietic stem cell transplants (HSCTs) are at risk of experiencing significant distress, including depression and anxiety [3,4], given the significant level of patient care that they need to provide. Patients receiving HSCTs require full-time care during the acute transplant and early post-transplant periods, as they face a compromised immune system and thus increased susceptibility to infections, as well as treatment side effects such as fatigue, insomnia, depression, anxiety, and sexual dysfunction [4-8]. As such, caregivers experience multifactorial stressors associated with caring for HSCT patients, leading to complex psychological outcomes that include depression and anxiety, and they are often reluctant to participate in support services given the extra time needed and the demands of their busy schedules. As a result, they can become "silent patients," being so overburdened with caregiving responsibilities that they neglect to take care of themselves. Furthermore, when the stress of caregiving becomes chronic, caregivers can be at higher risk of developing health problems, which can lead to poorer care for their loved ones [9]. Given the bidirectional nature of the caregiver-patient relationship, helping caregivers manage their stress not only may have beneficial results for the caregiver but also may improve patient outcomes. Thus, convenient access to brief, evidence-based resources is needed to help caregivers manage the stress associated with caregiving [10].

A recent study showed that a brief in-person stress management intervention was effective in reducing the distress of caregivers of patients receiving allogenic HSCTs (allo-HSCTs) [3]. This intervention provided strategies for enhancing the sense of perceived control over stressors inherent to caregiving, understanding role changes, and improving communication during and after transplantation. Additionally, another study assessed caregiver and patient requirements for interactive health communication applications (IHCAs) targeting long-term conditions as well as their criteria for assessing the quality of different programs [11]. IHCAs combine high-quality health information with interactive components (ie, self-assessment tools, behavior change support, peer support, or decision support) and are largely web based. Participants in the study had a favorable view of the potential for Internet interventions to assist with long-term caregiving [11]. However, based on a recent systematic review of Internet-based interventions for caregivers, there are no evidence-based stress management interventions designed specifically for caregivers of HSCT and cancer patients that can be widely disseminated (eg, through technological platforms) [10]. Despite the paucity of evidence-based technological interventions that aim to aid caregivers in managing their stress, 74% of caregivers report being interested in technology that would help them to manage the emotional stress associated with caregiving [12].

Mobile technologies can provide a convenient mode of dissemination for evidence-based resources for managing the stress of caregiving [13]. In a recent study examining caregivers of patients with cancer, most caregivers had access to technological means (eg, Internet and email), and the majority of the caregivers sampled acknowledged that they would potentially utilize caregiver support tools disseminated via the Internet [13]. For overburdened caregivers, mobile technology can provide a valuable source of support for daily self-care that is accessible in their home environment. Mobile technologies have also been effectively implemented as a stand-alone treatment, which is ideal for caregivers with multiple demands who need to care for patients at home [14-23]. As such, the development of an intervention that can be accessed using popular technologies (eg, smartphones, tablets) provides an innovative way to disseminate reliable, empirically supported treatments to caregivers of medically compromised populations who have limited access to in-person support services. In addition, many interventions require heavy resource utilization. Compared to in-person interventions, mobile technologies require fewer personnel resources to disseminate evidence-based treatments and thus may be more cost effective.

Evidence-Based Intervention

Cognitive-behavioral stress management (CBSM) is a therapeutic intervention that focuses on teaching cognitive and behavioral strategies for coping with cancer [24]. Studies of patients with breast cancer have demonstrated the efficacy of CBSM, with participants in the CBSM intervention groups reporting increased optimism [24], reductions in symptoms of

depression and increased ratings of quality of life [25], and improved psychological adjustment to illness [26]. Our previously reported intervention, PsychoEducation, Paced Respiration and Relaxation (PEPRR), was modeled after CBSM and effectively reduced perceived stress, anxiety, and depression in caregivers 3 months post-transplant [3]. However, as structured, the dissemination of that intervention was limited because it required caregivers to meet with a trained clinician in person, which necessitated travel time and schedule flexibility for appointments. Thus, PEPRR may be inaccessible or unacceptable to caregivers who are most in need, namely, those who are so overburdened with caregiving that they cannot participate in this in-person, evidence-based treatment.

Objective

The purpose of this study was to conduct formative research (eg, stakeholder groups) and pretesting (eg, focus groups and individual interviews) [27] to gather feedback on the look and feel, content, potential acceptability, anticipated usability, and feasibility of Pep-Pal, a mobilized, adapted version of PEPRR. The formative research was then used to inform the development of the final version of Pep-Pal and will be used to facilitate its dissemination.

Methods

For the purpose of this study, mock-up videos were models of videos (eg, prototypes) used to demonstrate the functionality of the Pep-Pal program and enable testing of the design with potential users. The mock-up videos were adapted based on previously suggested steps for developing and evaluating mHealth interventions [27]. This study followed these two steps: *Step One*, formative research with expert, patient, and caregiver stakeholder groups to develop a usable prototype to test with caregivers in the next step, and *Step Two*, pretesting of Pep-Pal mock-up videos with focus groups and individual interviews.

Setting

This study was conducted at the University of Colorado Denver Anschutz Medical Campus.

Step One: Formative Research With Expert, Patient, and Caregiver Stakeholder Groups

A Web-based animated video production service, GoAnimate, INC, was used to develop an initial prototype video session of Pep-Pal. This prototype session consisted of a brief, 10-minute psychoeducation video about stress and stress management delivered by an animated female character posing as a clinical psychologist with a human narrator. The video included content adapted from the PEPRR manual about understanding stress and how stress is experienced by caregivers as well as a brief description of how to manage stress [3]. The prototype video session ended with an animated caregiver character being guided through a body scan exercise. A variety of background music clips were used to enhance engagement.

We conducted three in-person stakeholder meetings, which included one professional stakeholder group (Group One, n=20) and two patient and caregiver stakeholder groups (Groups Two and Three, n=9 total). The professional stakeholder group was included to gather feedback about the acceptability and impressions of the program as well as the potential feasibility of disseminating the intervention. Institutional review board approval was not required for Step One because no demographic data were collected and because feedback was gathered during regular meetings (convenience sample) with experts, patients, and caregivers. Participants in the professional stakeholder group (Group One) included physicians, nurses, social workers, chaplains, and clinical psychologists from a local academic medical center who had expertise in palliative care. Participants in the other stakeholder groups (Groups Two and Three) included men and women between the ages of 30 and 65 who were caregivers of patients with various conditions, such as HSCT recipients. All stakeholder groups watched a 10-minute video example of a Pep-Pal session and provided open-ended feedback in a discussion format. Stakeholder meetings lasted approximately 60 minutes each.

In line with previous recommendations [27], feedback from the stakeholder groups was categorized into several domains: acceptability, anticipated usability, and feasibility. *Acceptability* was defined as the willingness of a user to use the program for its intended purpose. *Anticipated usability* was defined as the extent to which the intended audience could understand the program and find the program to be useful and meaningful. *Feasibility* was defined as the extent to which the program could be made readily available and implemented with the intended audience. In addition, feedback on the look, feel, and content was gathered to enhance acceptability.

Step Two: Pretesting of Pep-Pal Mock-Up Videos With Focus Groups and Individual Interviews

The goal of Step Two was to conduct focus groups and individual interviews with caregiver participants to assess the acceptability, anticipated usability, and feasibility of the Pep-Pal mock-up videos. Step Two of this study was approved by the University of Colorado Anschutz Medical Campus Institutional Review Board, and informed consent was obtained from all participants.

Procedure

Recruitment and eligibility for the focus groups and individual interviews included convenience sampling of caregivers of patients with auto-HSCTs; these caregivers were referred by the Bone Marrow Transplant Clinic and were recruited by phone. The inclusion criteria required participants to be caregivers of patients receiving auto-HSCTs, to be able to speak and read English, and to be at least 18 years of age. The exclusion criteria for caregivers included an absence of a psychiatric or medical condition preventing participation.

Focus Groups

A total of 6 Caucasian women who were spousal caregivers between the ages of 46 and 66 participated in the two focus groups. While 8 caregivers were recruited, 2 were unable to attend the focus groups due to their caregiving responsibilities. Notably, 1 caregiver who did not attend asked, “Is there something I can do online?”, supporting the convenience and accessibility of the intervention.

We conducted two semi-structured focus groups. The focus groups were 60 minutes each and were audiotaped. The caregiver participants in the focus groups watched two mock-up videos and provided opinions regarding the videos' look and feel, content, acceptability, anticipated usability, and feasibility. The first mock-up video included an introduction to Pep-Pal, which provided instructions about the purpose of the Pep-Pal program and how to best utilize the program. The second mock-up video was entitled "Session One: Introduction to Stress Management" and described introductory coping skills for managing stress.

Individual Interviews

Based on the results of the focus groups, nine videos of full-length sessions were developed, covering the following topics: introduction to stress management, stress and the mind-body connection, how our thoughts can lead to stress (cognitive distortions), strategies for maintaining energy and stamina, coping with uncertainty, managing relations and coping with your needs, getting the support you need, and improving intimacy. Each Pep-Pal session was less than 10 minutes. Before conducting the individual interviews, two trained clinicians from the original PEPRR study [3] reviewed the Pep-Pal videos and independently both rated the videos as covering all topics from PEPRR. This step was integral to confirming the integrity of Pep-Pal's adaptation from an evidence-based intervention that effectively reduced symptoms of anxiety, depression, and perceived stress in caregivers of allo-HSCT patients.

We conducted individual interviews with the caregivers of auto-HSCT patients to gather specific feedback on the nine video sessions as well as the overall Pep-Pal program. Participants completed a semi-structured interview that assessed five primary domains: (1) the look and feel of the video sessions, (2) the content addressed in the video sessions, (3) the anticipated usability of the video sessions, (4) the acceptability of the video sessions, and (5) the feasibility of the overall program. Participants were asked about their overall impressions of the sessions, what they may have found helpful or unhelpful in each session, their level of comfort in navigating through the videos, and whether they would consider watching the videos again to review the skills. They were also prompted to provide suggestions for any topics that needed improvement or needed to be added to better serve their needs. Each participant completed a 90-minute, semi-structured interview that consisted of watching an introductory video as well as three other sessions. The interviews were audiotaped and transcribed. At the beginning of the interview, participants were given the choice to watch the sessions on a laptop, tablet, or smartphone. Overall, 8 participants (8/9, 89%) chose to use a laptop, 0 participants used a smartphone, and 1 participant (1/9, 11%) used a tablet to view the videos. We analyzed the interviews after the entire data collection process was complete. Participants were white spousal caregivers (n=9) with a mean age of 59.3 and were predominantly women (n=7).

Data Analysis

Applied thematic analysis, which is a thorough yet inductive qualitative approach, was conducted for each interview to identify themes [27]. The first and second authors (NAP and TJ) independently reviewed the transcripts and discussed the themes emerging from the data. They then applied open coding to the transcripts and developed an initial codebook. After discussing the codebook and agreeing upon the codes, TJ coded all transcripts independently and finally identified broad themes within each domain. These themes were then used to further develop and refine the Pep-Pal program. Data saturation was reached when no new themes emerged regarding the look and feel, acceptability, anticipated usability, and feasibility.

Results

Step One: Results of Formative Research With Expert, Patient, and Caregiver Stakeholder Groups

Patients, caregivers, and professional stakeholders provided feedback regarding the look and feel, content, acceptability, anticipated usability, and feasibility of Pep-Pal in order to develop an improved prototype for Step Two. Feedback from stakeholders ranged from "*I love what you are trying to do here to meet the needs of caregivers*" to "*this seems like one more thing for caregivers to do.*" In addition, patients, caregivers, and expert stakeholders wanted more introductory information added to explain the benefits for caregivers. The stakeholders preferred a mix of animated and human delivery of information on-screen. Finally, technical feedback included "*the music is too fast"* and suggestions to provide more information on respite and other resources earlier in the intervention program. In response to the feedback, the program was modified to enhance its acceptability and anticipated usability. See Table 1 for a summary of the feedback from the stakeholder group meetings and the changes made to refine the Pep-Pal prototype.

Refining of Pep-Pal Prototype

Several changes were made to the prototype based on the feedback gathered from the three patient, caregiver, and expert clinician stakeholder meetings. These changes to the prototype then informed the pretesting. The most important addition was the creation of a separate introductory video to orient the caregiver to the purpose of the Pep-Pal program and to how best to utilize Pep-Pal. In terms of content and anticipated usability, instructions were added to the introductory video, explaining that Pep-Pal should not replace any in-person support; rather, Pep-Pal should be used in addition to professional support or in the interim, until further support can be accessed. In the video, caregivers were also encouraged to ask for more support from their providers as needed. To improve the look and feel, specific features of the main animated character in Pep-Pal were changed (eg, different hairstyle and smaller eyes). In addition, more human-delivered content was filmed based on the reported preferences of the stakeholders. In terms of content, the topic of Advance Care Planning was removed because it was deemed to be beyond the scope of this intervention.

Other modifications included changing the background music to have a more relaxing "feel"; slowing the pace of the videos; and adding content, including the recommended "dosage" of Pep-Pal (eg, watch each session at least once, for no more than two sessions per week initially, and then watch the videos in

order of personal preference) and content encouraging caregivers to "take care of themselves first." Major and minor changes resulted in the development of two prototype mock-up videos for pretesting in Step Two: (1) Introduction to Pep-Pal and (2) Introduction to Stress Management.

Table 1. Summary of feedback from stakeholder group meetings and changes made (Total N=29).

Theme	Patients and Caregiver Stakeholders (n=9)	Professional Stakeholders (n=20)	Changes Made to Pep-Pal
Look and Feel	Music • "too loud" • "too fast-paced" • "make calmer" Animation • "don't like the animated character's eyes" • Like the mix of human and animation • Prefer real person on-screen Scenes • Like the "hospital room scenes"	Music • "too intense and loud" Visual Displays • Change "PEP-PAL" to "Pep-Pal" • Change "Mini-PEPS" to "Mini-Peps" Pace • "Too fast"	• Background music changed to be softer, calmer, and slower • Changed main animated character • Added more human-delivered content • Changed PEP-PAL to Pep-Pal • Changed Mini-PEPS to Mini-Peps • Slowed down session
Content	Tone • Include positive and negative examples of change • Tone down negative symptoms • Change "stress" to "stress management" to portray a more positive tone Information • Include information about "diet, complications, chat forum, grief, book recommendations, and community resources" • Provide norms of caregiving challenges • "Give more of an introduction" • "Shorten list of symptoms" • Give caregivers "permission to take care of themselves"	Information • Delete long information section • State "how to best take care of your loved one" • "Encourage caregivers to ask for more support from their providers" • Use sponge metaphor to explain self-care • Get rid of Advance Care Planning: "too complicated" • "Introduce team"	• Deleted long information section and negative examples • Added encouragement for caregivers to ask for more support from their providers • Changed "stress" to "stress management" • Took out Advance Care Planning • Introduced on-screen care delivery team • Added introductory session video • Shortened list of symptoms • Added content for caregivers to give them "permission to take care of themselves"
Acceptability	• "Program will be helpful and convenient" • "This seems like one more thing for caregivers to do."	• "The video is great!" • "The introduction is really good." • "I love what you are trying to do here to meet the needs of caregivers."	
Anticipated Usability	Timing of Delivery • Deliver video right after diagnosis • Offer intervention as early as possible Usage • Caregivers can watch the videos in the hospital • Seems like "one more thing" • Can be used by the patient and caregiver together • Caregivers will watch this at different stages	Usage • Can be used in a "variety of caregiver populations" (eg, dementia patients, oncology patients in Phase I clinical trials) • "Can you provide email reminders?"	• Feedback noted for final dissemination
Feasibility		• Like that it will be tested in a natural usage setting • Define minimum dosage of videos (eg, 75%; 1-2 times per week)	• Defined recommended dosage as follows: watch each session at least once, no more than 1-2 sessions per week for first-time views; afterward, can re-watch as many times as wanted

Table 2. Summary of major iterations to Pep-Pal after focus groups.

Theme	Focus Group Feedback (N=6)	Iterations Made
Look and Feel	• Majority preferred mix of animated ("keeps it light") and human ("provides credibility") delivery • Pace was too fast • Background music was relaxing	• Kept a mix of animated and human content delivery • Slowed pace • Used relaxing music throughout all sessions
Content	• "Helps you become aware of what's going on with your body." • "Easy to understand." • "Include more positive examples."	• Kept body scan video and information about bodily sensations • Added more positive caregiving examples
Acceptability	• "I wish it was available now." • "...could use it in the waiting room"	• N/A
Anticipated Usability	• "Include more step-by-step instruction in the body scan video." • Include breathing exercises	• Added more step-by-step instructions to all videos • Added deep-breathing exercise
Feasibility	• Would like email reminders to complete the sessions throughout the week • "Very convenient." • "A website would be great."	• Noted to include reminders and make sessions available on a website platform to facilitate final program dissemination in the pilot randomized controlled trial (RCT)

Step Two: Results From Focus Groups and Individual Interviews

Focus Groups

A summary of the major feedback from the Step Two focus groups is summarized in Table 2 (below). The feedback from the focus group participants was then integrated into the refinement and development of the nine Pep-Pal sessions to be tested in the individual interviews. The focus group participants were asked a series of questions about the program's look and feel (eg, about the animated characters, music, length, and pace), anticipated usability (ie, satisfaction with the program and clarity of the instructions), and feasibility (ie, how they would use the program).

Individual Interviews

Themes were analyzed across each category for look and feel, content, acceptability, anticipated usability, and feasibility. Table 3 (below) summarizes the major themes and feedback gathered from the individual interviews.

Summary of Results From Individual Interviews

Overall, 9 participants, who were caregivers of patients who had undergone auto-HSCTs, participated in the individual semi-structured interviews and provided their thoughts and feedback on the Pep-Pal program. The interviews assessed domains including the look and feel, content, anticipated usability, acceptability, and feasibility. Different themes emerged, and the feedback gathered was further integrated to inform the development of the final version of the Pep-Pal program. A summary of the results of the qualitative interviews and changes implemented in the final version of the Pep-Pal program is provided in Table 4.

Table 3. Qualitative thematic analysis.

Themes and Subthemes	Quotes
Look and feel	
Animation versus human	"It's like you almost didn't value the material enough. The medium does not match the message...I think you need to value the message more."
	"I was distracted by some of the animation...It caused me to actually concentrate on the corny animation and lose the thread of what was being said."
Distractions	"I was watching more the movement and then the words kind of disappearing rather than listening to what it was–I mean, really ascertaining to what it was talking about."
Content	
Need for personalized examples	"I was trying to connect it [the session] to caregiving, and I was having trouble connecting this particular one to caregiving. I know you did several times use the word caregiver in this, but for me, I was struggling to connect."
	"I was wondering, does it [the intervention] go into more specifics about the types of stress that come up? Like specifically when they lose all their body hair or you can't use their bathroom because the chemicals are in there and that's dangerous?"
	"And they [caregivers] have a fair amount of stress. And not only the ordinary kind of stresses about 'How do I maintain a healthy attitude?' and so on but things like, 'Should we sell this house and move to assisted living?...Who do I ask for help?'"
Validating the caregiver experience	"I've had people tell me it's harder to be the caretaker than to be the one with the cancer...while I certainly can't speak to that because I have not been in the other role, it is a very difficult thing, and so it's nice to have something for us to help us serve, 'cause it is a very challenging situation to be in."
	"I think caregivers ask, 'Am I the only one who's having this kind of stress or having this intimacy problem?' But when you address it like this [the program], it helps because then you're not afraid to realize that you can talk to somebody because other people are going through it too or it wouldn't be included in here."
Combination of one-on-one support and the program	"One of the things that would be helpful to reiterate during the different components [of the program] is that the caregiver doesn't have to have all the answers, and if there is something that's unclear or doesn't make send or is causing stress, just a reminder to go back to the health care providers."
	"You sit down in front of it [the program]. You've got choices to watch it, stop it, fast-forward it. But you really can't say, 'Wait a minute. Could you explain that in more detail?'"
Usability	
No difficulty independently navigating sessions	"I couldn't really tell whether they were encouraging you to do it now or just to file it away for later"
	"I was kind of confused: like should you push STOP and then go ahead and then make a list right then? Or kind of the directions, like, 'Okay, if you want to, you can push STOP now and go ahead and make that list or continue on.'"
Acceptability	
Caregivers felt this was an acceptable way to get support	"I would [use the program]. Yeah, I'd feel like it would be really, really helpful."
Brevity of the sessions and flexibility	"Sometimes you don't have the time to do anything more than a ten-minute session...things [in the program] are repeated, and it's like, 'Oh yeah, I forgot that, let me go back and look at that one.'"
Feasibility	
Program introduction early on during the diagnosis	"I think maybe [introducing the program] in the beginning [of diagnosis]. But then I think also it needs to be kind of–in the beginning, there is so much overwhelming stuff that's going on that it would be ignored. So it should be like brought up again in a month and brought up again. And just kind of have it available. 'Cause I think there's parts of it that I think–especially the relaxation and breathing stuff–that would be so helpful right initially. But I also think that it would be something that could get filed away on a shelf. But it's nice 'cause it's always there. I mean, it's very portable, very accessible anytime."
The need for the program to not be dependent on the Internet	"I think having it [the program] on an Internet interface would be the really appropriate way to go, but there might be situations where Internet access isn't that available. You might think about having a separate option where you could download it."

Table 4. Summary of qualitative interview results and iterations to Pep-Pal program to obtain final version.

Theme	Individual Interview Feedback (N=9)	Iterations Made
Look and Feel	• Majority preferred human-delivered content • Include text on-screen • Use simple graphics so as to not distract viewer • Use more relaxing and softer music	• Final Pep-Pal videos include all human-delivered content conveyed by a variety of human clinicians • Used simple text and graphics • Changed music to be more relaxing and softer
Content	• Include more specific caregiver examples • Include suggestions for contacting health care providers	• Specific caregiver examples were added throughout each session • Actress hired to portray caregiver on-screen and to go through examples in each session • Caregivers encouraged to speak with health care providers • Information for national support resources provided
Acceptability	• Want to be able to go back and watch at any time	• Easy access to videos is provided (eg, just click this button to watch again at any time)
Anticipated Usability	• Add more instructions to videos (eg, stop, pause, do this activity along with video) • Liked that the program was not linear, so could watch sessions in any order • Pace was too slow in introductory session • Pace was too fast in relaxation exercise video	• Instructions added throughout • Videos not suggested to be viewed in any specific order, but all videos have to be watched at least once • Pace was increased in introductory session • Pace was slowed in relaxation exercise video
Feasibility	• Want to be able to watch videos anywhere (eg, waiting room, bathroom, during medical appointments) • Include weekly email reminders to use Pep-Pal • Offer program to caregiver at time of diagnosis	• Website must be mobilized to enable access on smartphone, tablet, or laptop • Automated weekly email reminders are provided with Pep-Pal

Discussion

Principal Results

The results from the stakeholder groups, focus groups, and individual interviews supported the acceptability, anticipated usability, and feasibility of Pep-Pal. Feedback was integrated into the final version of Pep-Pal. We found that the domains of usability, acceptability, and feasibility were strongly related to content; when the content resonated with participants, their ability to use the program, willingness to accept the program, and faith in the feasibility of the program increased.

We integrated feedback from Step One, encompassing formative research with expert, patient, and caregiver stakeholder groups, and Step Two, encompassing pretesting of the Pep-Pal mock-up videos with focus groups and individual interviews, into the final version of the Pep-Pal program, which will be tested in a pilot study in Step Three. This process was suggested by Whittaker et al [26] for the development and evaluation of mHealth interventions. Currently, Pep-Pal is available on a mobilized website (eg, can be viewed on a smartphone, laptop, computer, or tablet) that hosts the full-session videos, Mini-Pep videos, and information about the research team. Mini-Peps are brief, 3-minute exercises (eg, related to relaxation, mood boosting, or relationship enhancement) that can be conveniently accessed if the caregiver does not have time to watch a full-session video. Mini-Peps were included in the full-session videos during the formative development study described here. The website is password protected and available only as part of the ongoing pilot RCT to assess the preliminary estimates of efficacy and obtain further information regarding acceptability, anticipated usability, and feasibility. A total of 60 caregivers of patients with advanced illness will be enrolled in this study.

Limitations

Several limitations were present. First, the patient and caregiver stakeholders were volunteers as part of research advisory groups and thus may represent participants who are more motivated than hard-to-reach or more vulnerable caregiver populations. Second, the developer of the Pep-Pal intervention coordinated the stakeholder groups, focus groups, and individual interviews, so participants may have been reluctant to provide more critical feedback. Third, all participants were white spousal caregivers, which may limit generalizability. Fourth, due to time constraints, detailed demographic data, including socioeconomic status and education level, were not gathered from all participants, thus further limiting the generalizability of this study. However, future studies will gather detailed demographic information. Fifth, the focus group sample size was smaller than anticipated (n=6 per group), and each group was composed of white women, introducing bias as a consequence of the selection of respondents. Finally, participants could not watch all sessions due to time limitations, and thus, saturation was not reached in terms of content. In the corresponding RCT, the developer of Pep-Pal will not conduct the qualitative interviews, the quantitative assessments will be completed on the Web, participants will be representative of more hard-to-reach caregiver populations, and participants will have access to all videos.

Future Directions

Pep-Pal is being testing in a pilot RCT with caregivers of patients with advanced illness (eg, patients with illness warranting an HSCT, patients with advanced cancer, and those in Phase I oncology trials) to determine the acceptability and feasibility of and preliminary efficacy estimates for Pep-Pal to reduce symptoms of anxiety, depression, perceived stress, and sexual dysfunction. Ultimately, the goal is to conduct a multi-site efficacy RCT of Pep-Pal with caregivers to facilitate future widespread dissemination of Pep-Pal.

Acknowledgments

Funded in part by grants from NIA T32AG044296 (JK to NAP) and NCI CA126071 (MLL) and a contract from PCORI CE1304-6208 (MLL).

Conflicts of Interest

None declared.

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Abbreviations

Allo-HSCTs: allogeneic hematopoietic stem cell transplants
Auto-HSCTs: autologous hematopoietic stem cell transplants
CBSM: cognitive-behavioral stress management
IHCAs: interactive health communication application
PEPRR: PsychoEducation, Paced Respiration and Relaxation
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 30.11.16; peer-reviewed by J Zhao, M Coleman; comments to author 19.01.17; revised version received 27.02.17; accepted 31.03.17; published 22.06.17.

Please cite as:
Pensak NA, Joshi T, Simoneau T, Kilbourn K, Carr A, Kutner J, Laudenslager ML
Development of a Web-Based Intervention for Addressing Distress in Caregivers of Patients Receiving Stem Cell Transplants: Formative Evaluation With Qualitative Interviews and Focus Groups
JMIR Res Protoc 2017;6(6):e120
URL: http://www.researchprotocols.org/2017/6/e120/
doi:10.2196/resprot.7075
PMID:28642213

Original Paper

An Interactive, Mobile-Based Tool for Personal Social Network Data Collection and Visualization Among a Geographically Isolated and Socioeconomically Disadvantaged Population: Early-Stage Feasibility Study With Qualitative User Feedback

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Abstract

Background: Personal social networks have a profound impact on our health, yet collecting personal network data for use in health communication, behavior change, or translation and dissemination interventions has proved challenging. Recent advances in social network data collection software have reduced the burden of network studies on researchers and respondents alike, yet little testing has occurred to discover whether these methods are: (1) acceptable to a variety of target populations, including those who may have limited experience with technology or limited literacy; and (2) practical in the field, specifically in areas that are geographically and technologically disconnected, such as rural Appalachian Kentucky.

Objective: We explored the early-stage feasibility (Acceptability, Demand, Implementation, and Practicality) of using innovative, interactive, tablet-based network data collection and visualization software (OpenEddi) in field collection of personal network data in Appalachian Kentucky.

Methods: A total of 168 rural Appalachian women who had previously participated in a study on the use of a self-collected vaginal swab (SCVS) for human papillomavirus testing were recruited by community-based nurse interviewers between September 2013 and August 2014. Participants completed egocentric network surveys via OpenEddi, which captured social and communication network influences on participation in, and recruitment to, the SCVS study. After study completion, we conducted a qualitative group interview with four nurse interviewers and two participants in the network study. Using this qualitative data, and quantitative data from the network study, we applied guidelines from Bowen et al to assess feasibility in four areas of early-stage development of OpenEddi: Acceptability, Demand, Implementation, and Practicality. Basic descriptive network statistics (size, edges, density) were analyzed using RStudio.

Results: OpenEddi was perceived as fun, novel, and superior to other data collection methods or tools. Respondents enjoyed the social network survey component, and visualizing social networks produced thoughtful responses from participants about leveraging or changing network content and structure for specific health-promoting purposes. Areas for improved literacy and functionality of the tool were identified. However, technical issues led to substantial (50%) data loss, limiting the success of its implementation from a researcher's perspective, and hindering practicality in the field.

Conclusions: OpenEddi is a promising data collection tool for use in geographically isolated and socioeconomically disadvantaged populations. Future development will mitigate technical problems, improve usability and literacy, and test new methods of data

collection. These changes will support goals for use of this tool in the delivery of network-based health communication and social support interventions to socioeconomically disadvantaged populations.

(JMIR Res Protoc 2017;6(6):e124) doi:10.2196/resprot.6927

KEYWORDS

social networks; social network analysis; personal networks; mobile surveys; survey development; survey implementation; low literacy; health disparities; rural health; Appalachia; cancer screening; diffusion of innovations

Introduction

Social science research has established the powerful role that our personal social networks play in our lives [1]. The structure and content of our social networks provide (or restrict) opportunities for access to information and resources, social support, social capital, exposure to norms and behaviors, and other mechanisms that consequently impact our behavior, health outcomes, and success [2-5]. Our networks impact how long we live [6-8], how healthy we are [9-12], what health information and resources we have access to, and how we are able to use these to support our health [13,14]. However, in order to understand this structure and measure the impact of networks on the lives of individuals and communities, we need to properly collect and analyze network data. While data from online social networking sites can be obtained to analyze online network behavior, collecting data about a person's *real* personal social network is an entirely different endeavor.

In ego network analysis (a subset of social network analysis) research focuses on an individual's personal network, which consists of the immediate contacts (alters) connected to an individual subject (ego) [1,15]. For example, an ego network may consist of the people one individual relies on for social support, or seeks health advice from. This approach is different from a whole network or sociometric approach, which analyzes an entire bounded network (eg, the network of romantic relationships in a specific high school, or a network of organizations in a coalition advocating for health policy). In a sociometric study of a bounded network, each network member that is surveyed provides information about his or her self and his or her direct ties to other specific individuals who are members of the same bounded network. For example, a student is presented with a roster of all students in his or her grade, and is asked to indicate with whom he or she eats lunch with at least once a week, or seeks advice from for a specific topic. In an ego network study, the subject is expected to provide not only information about his or her self and his or her direct ties to alters, but also details about each of his or her alters and the relationships or ties between these alters.

To reach a wide and diverse sample of network members, some researchers ask broad *name generators* such as, "name 25 people you know" which may or may not be followed with a prompt for more specific relationships or context to consider during recall. After the names of the alters are generated, the subject is asked to provide descriptive information about each of the alters via *name interpreter* questions. This descriptive information is often sociodemographic (eg, gender, relative age, or education) or evaluative (eg, how much do you trust health information from this person, how frequently do you discuss personal matters with this person). These descriptive questions scale linearly with the number of alters. For each additional alter an ego provides, the ego must answer one additional response per question to describe the new alter. To ascertain some information about the structure of an ego network, the respondent may also be asked to describe the relationships between each *pair of alters* in their network. For example, if ego Bob names Mary and John as alters in his network, then Bob may be asked whether Mary and John talk to one another when Bob isn't around. This allows researchers to understand which of the alters in the ego's network are connected to one another as well as to the ego. However, the number of *alter-alter tie* questions scale with the square of the number of alters.

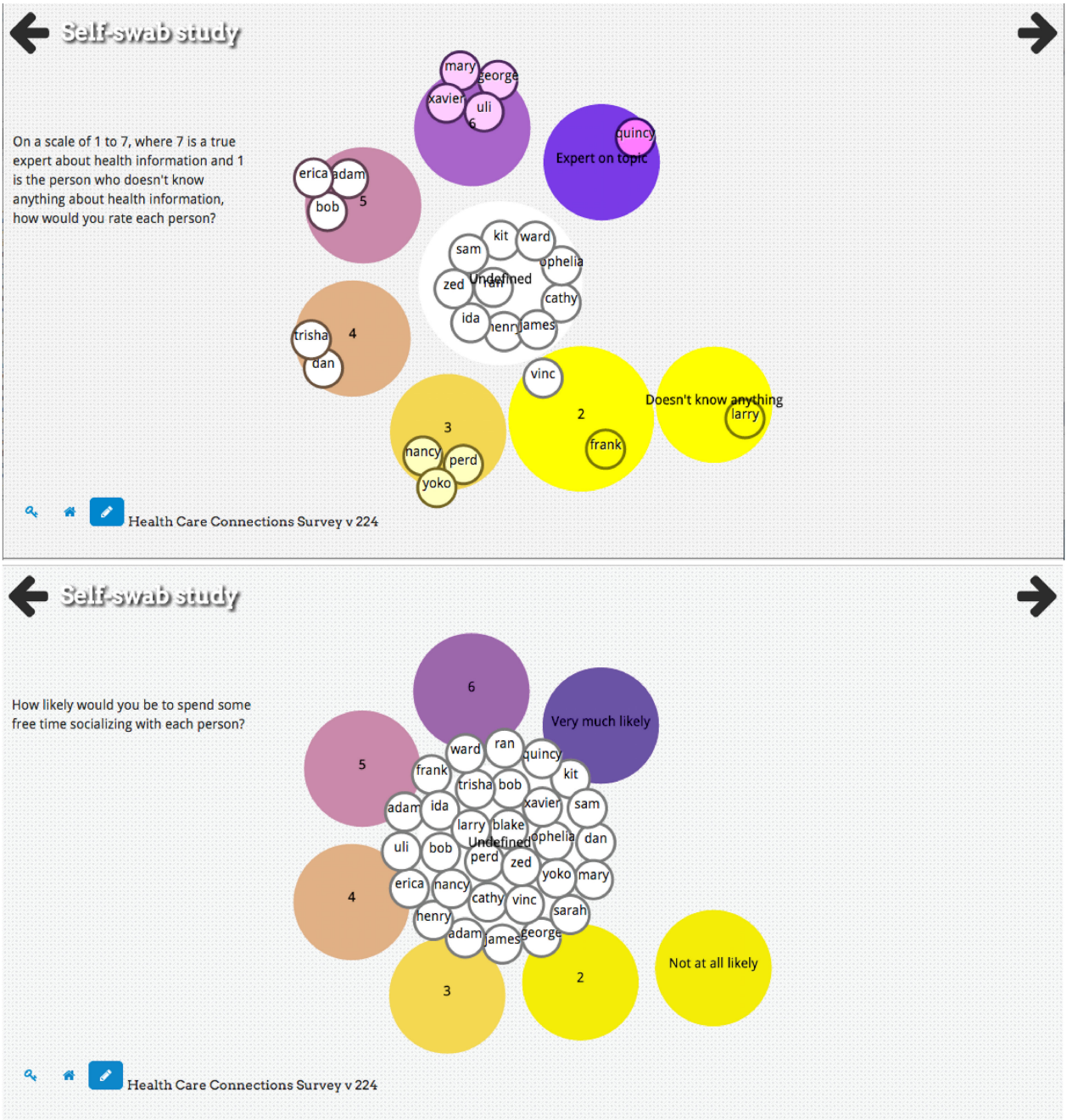
Network data collection often provides a tremendous burden on respondents who have larger networks, and as a result scientists may restrict the number of alters an ego can name (which may or may not decrease the richness and value of data collected, depending on the research question) or eschew network data collection entirely. In addition, this burden can discourage interviewers from allowing respondents to report higher numbers of alters, resulting in interviewer effects on network size [16,17]. Respondents may also be discouraged from naming alters, particularly in longitudinal studies in which a respondent may learn that naming fewer alters in subsequent interviews results in fewer questions, and minimizes the time needed to complete a survey.

Fortunately, in the past decade, advances in social network data collection and visualization software have reduced the burden of network data collection for researchers and respondents alike, particularly for ego or personal network studies [18-24]. The next step is to understand how well these advances work in the field, including whether they: (1) function as intended; (2) are able to accurately, reliably, and efficiently represent the personal networks of respondents; (3) are acceptable to a variety of target populations, including those who may have limited experience with technology or limited literacy; and (4) are practical in the field, specifically in areas that are geographically and technologically disconnected. While some investigation and testing of the functionality and data quality produced by these tools have been explored in the literature, the last two points—acceptability by target populations and practicality in the field—are of particular interest to researchers whose work is focused on reaching marginalized, socioeconomically disadvantaged populations, and connecting them to health services, support, and solutions.

We explored the feasibility of using interactive, tablet-based network data collection and visualization software (OpenEddi) in field collection of ego network data in Appalachian Kentucky, which is a geographically and technologically isolated

population with population-levels of education and literacy well below the national average [22,25]. We followed the recommendations of Bowen et al [26] in assessing feasibility during an initial phase of intervention development. To do so, we want to answer the question, " *Can it work?* " The goal of this paper is to describe the acceptability, demand, implementation, and practicality of using this software in the context of a health communication study. Quantitative data was collected via implementation of the tool, and the qualitative experience of Appalachian research participants and interviewers was also examined. We aimed to demonstrate the benefits and challenges of using OpenEddi and a network visualization approach in this population and setting, thereby informing long-term goals of applying OpenEddi as a tool to facilitate the delivery of network-based health communication and social support interventions.

Figure 1. Examples of an alter characteristics bubble sort, which is used to assign alter attributes.



Background

OpenEddi Data Collection Tool

OpenEddi is an adaptable, modular survey software platform designed for interactive, tablet- and mobile-ready field collection of network data, with or without an Internet connection. The platform was created to reduce the burden of network data collection on both the participant and the interviewer by using visuals to simplify the process of identifying and characterizing alters (Figure 1) and alter-alter ties (Figure 2), which may also improve reliability and validity of network data [27]. More detail on OpenEddi can be found in Multimedia Appendix 1. This paper reports the use of OpenEddi Version 0.2. We continue to develop and improve the software to best meet user

needs. A video of Version 0.3, which is in development, can be viewed in Multimedia Appendix 2.

OpenEddi question types fit into five broad categories: (1) general survey questions or ego characteristics, (2) network identifiers (name generators, rosters, name interpreters), (3) alter characteristics, (4) relationship or tie characteristics, and (5) ties between alters. Alter attribute and relationship characteristic questions may be asked alter-by-alter (ask all questions about each alter before moving to the next alter) or question-by-question (ask a single question and respond for all alters before moving to the next question), or can alternate between both approaches. The program is ideally suited for the question-by-question format, which may produce more reliable and valid data [27].

Figure 2. Example use of pile sort feature to elicit ties between alters.

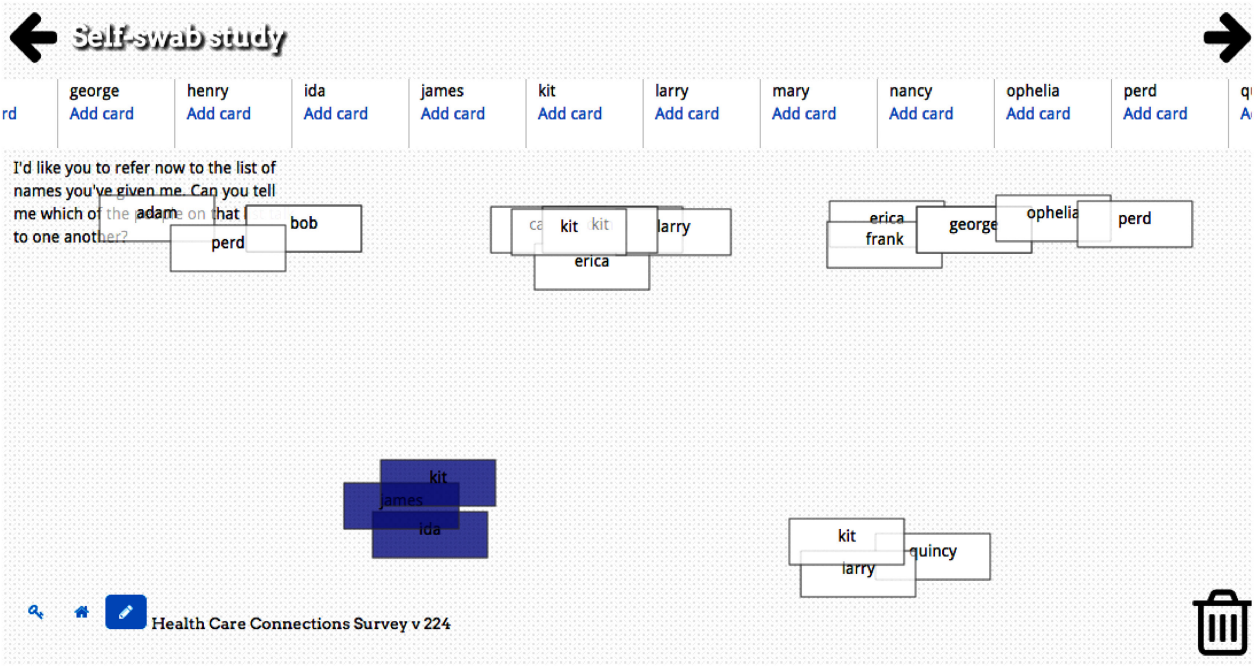
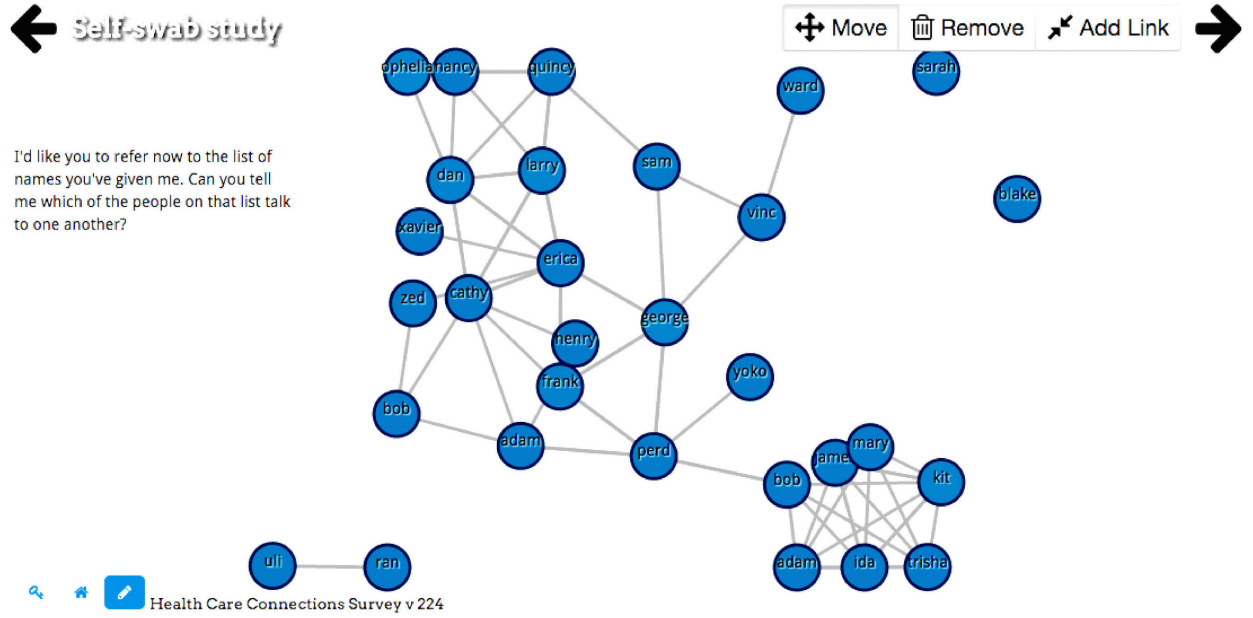


Figure 3. Example of nodelink diagram representation of participant network with ties between alters. Users may also use the nodelink diagram to add or delete these ties.



Creating a tool that is accessible to those who may have lower literacy, computer literacy, or education was an important goal in designing OpenEddi. User interface design for low literacy populations has focused on simplifying visual and audio approaches. OpenEddi employs a simple user interface design, including having *back* and *forward* buttons for navigation, as well as a *home* button rather than drop-down menus; this linear navigation can make digital tools more accessible for low-literate populations [28,29]. Radio buttons and large visual icons are recommended tools for use with nonliterate or

low-literate populations [29], as are text-to-speech and audio input tools [30]. Colorful shapes, large buttons, questions that are answered by dragging bubbles into groups, and dynamic network graphical displays (Figure 3) are all examples of how OpenEddi uses playful design to gamify the data collection experience. Additional examples of OpenEddi's user interface can be seen in Multimedia Appendix 3.

Other scalable, open-source mobile health data collection tools have been created with flexible platforms (eg, Survalytics [31], Beiwe [32]) for offline field collection of data using culturally appropriate means [33], and for using visual-based representations of standard survey question types in order to reach those with lower health or technological literacy (eg, Pit-A-Pat [34]). OpenEddi is the first platform to combine these three features with the ability to collect social network data (sociometric and personal) to create a powerful system for engaging populations who are often deemed "hard to reach" with traditional data collection means and methods.

Parent Study Population and Context

The easternmost third of Kentucky is considered part of the Appalachian mountain range, and contains some of the most unhealthy and poorest counties in the United States [35]. Kentucky has the highest rates of cancer mortality in the United States, and in the Appalachian Kentucky River Area Development District (KRADD), where our study was conducted, the cancer mortality rate is 41% higher than the national rate [36]. Associated with this unequal burden of cancer is the fact that Appalachian women are less likely to be screened for cancer within recommended guidelines, compared to non-Appalachians [37-42].

Education and health literacy are far below average in Appalachian Kentucky; 43% of adults in the KRADD have less than a high school diploma or equivalent, compared to 25.9% of Kentuckians and 19.6% of US adults [43], and this level of education is nationally correlated with having below-basic health literacy [44]. Some effort has been made to adapt health research and community engagement tools to address this communication barrier, yet there remains a need for easy-to-understand, enjoyable tools to reach populations with low education and literacy.

The mountainous terrain of Appalachian Kentucky, along with a history of economic depression, has resulted in a population that is geographically, technologically, and economically isolated, leaving Appalachian residents difficult to reach with roads, telephone, Internet, food, jobs, and health and social services. However, this same terrain shapes close-knit kinship and community ties, social cohesion, and a strong sense of native Appalachian heritage that result in powerful social support networks in Appalachian communities [45,46]. These networks, while strong in emotional support, are limited in access to formal social, health, and economic resources. Few studies have examined how network ties in Appalachian communities might be used to communicate information and norms about cancer screening and prevention behaviors, but those that do have uncovered network structures conducive to information diffusion by change agents and a willingness of Appalachian *key players* (or opinion leaders) to assume this role [38,47].

We conducted a pilot study to explore peer word-of-mouth communication networks in rural Appalachian women who interacted with an innovative screening method for high-risk strains of human papillomavirus (HPV) that cause cervical cancer, to better understand how to activate networks to disseminate innovative cancer screening and prevention information. After this study concluded, we conducted an informal qualitative group interview to obtain feedback on participant and interviewer experiences using OpenEddi. Quantitative data from the network study and its implementation, and qualitative data from the group interview, are examined in this paper to assess the feasibility of using OpenEddi to successfully collect social network data in a geographically isolated population of rural Appalachian women. Results will guide iterative development of OpenEddi as a method and intervention tool, moving toward further feasibility and efficacy trials.

Methods

Study Setting and Participants

The Rural Cancer Prevention Center (RCPC), a federally-funded Prevention Research Center, conducted a study in which rural Appalachian women used a self-collected vaginal swab (SCVS) for HPV testing [48]. This study will hereafter be referred to as the *SCVS study*. A total of 400 women between the ages of 30-65 years who resided in rural Appalachian Kentucky, were sexually active, reported no Papanicolaou test in the past three years, and reported never testing positive for HPV, participated in this study. Women were recruited through flyers in health departments, community outreach events, and other health care settings. Women in this study reported an average age of 40.2 years (standard deviation [SD] 9.3), most reported their ethnicity as white (94%), and most had a monthly income of less than US $1000 (59%).

We trained four nurse interviewers (all native to the KRADD and employed by the RCPC) to use OpenEddi to obtain information about participants' egocentric social support and communication networks. This study will hereafter be referred to as the *network study*. Any woman who had participated in the SCVS study and agreed to be contacted for future studies was eligible for recruitment into the network study. Interviewers recruited individuals via telephone or in person. Women who agreed and consented to participate were interviewed using iPads at a location chosen by the participant between September 2013 and September 2014. Given very limited access to the Internet in rural KRADD, it was important that the interview and data collection could be conducted without an Internet connection. Interviewers administered the nonnetwork portion of the survey to participants verbally and recorded participants' responses. For the network questions, the interviewer turned the tablet over to the participant and provided guidance as the participant navigated the survey interface herself. In some cases of very limited literacy or vision, the interviewer read most or all of the questions.

The final screen of the survey displayed the names the participant provided in response to a question regarding with whom she discussed the SCVS study. Participants were then

provided cards with their study identification number and the interviewer's contact information, with a request to have these identified network members call the interviewers to participate in the study, which resulted in the recruitment and enrollment of up to three of any participant's network members. This *second wave* of individuals was recruited, and those who consented received one of two surveys: (1) if she also participated in the SCVS study, she received the identical survey administered to first wave participants; or (2) if she had not participated in the SCVS study, she received a similar network survey with differences in questions pertaining to the SCVS study (eg, eligibility for SCVS, why did she not participate if eligible) and the inclusion of sociodemographic information that we did not have access to via the SCVS study. Study participation concluded after the single interview session.

We conducted an informal qualitative group interview of all four nurse interviewers who had administered the network survey to respondents, and two women who participated in the network survey, to better understand the user experiences of OpenEddi in this setting. All of the women in attendance lived in the KRADD. The four nurse interviews comprised 100% of the interviewers in the network study. The two network study participants were recruited by the nurse interviewers to voluntarily participate in this qualitative group interview, to provide feedback on the software and their participation in the network study, and represent a small convenience sample of the total population of network study participants. We conducted this qualitative group interview in May 2015 at the Perry County Extension Office in Hazard, Kentucky. The authors served as moderators and took notes electronically to record responses. Open-ended prompts were used to elicit feedback from group members. There was no audio recording of the group. However, responses quoted in the results section are reported as accurately as possible. While the authors prepared an informal interview guide of topics to address in advance, the discussion evolved organically and was led primarily by the participants, with prompts from the authors. We did not develop formal coding strategies for the interview notes; the authors discussed the interview responses and synthesized themes together.

The University of Kentucky Institutional Review Board (IRB) approved both the parent SCVS study and the network study. While IRB approval was not obtained before conducting the informal qualitative group interview, permission was granted by the University of Kentucky IRB to use the resulting data in publications and presentations.

Description of Network Survey

Nonnetwork questions (on topics such as health communication, health care access, social capital, political engagement, and innovative screening method for HPV) were asked first, followed by the ego network survey. A description of the ego network survey components, and how they are presented and used in OpenEddi, can be found in Multimedia Appendix 1.

Feasibility Measures

We stated that the next step in developing innovative technologies for network data collection is to understand how well these advances work in the field. We used guidelines from Bowen et al [26] to assess this feasibility in four areas of early-stage development of OpenEddi: *Acceptability*, *Demand*, *Implementation*, and *Practicality*.

Acceptability

"To what extent is a new idea, program, process, or measure judged as suitable, satisfying, or attractive to program deliverers? To program recipients?" [26]. Outcomes of interest for acceptability of OpenEddi include: (1) are interviewers and participants satisfied with their experience using OpenEddi?; (2) is OpenEddi perceived as appropriate for use in a rural Appalachian population?; and (3) does the use of OpenEddi fit in the organizational setting of the interviewers?

Demand

"To what extent is a new idea, program, or measure likely to be used?" Outcomes of interest for demand of OpenEddi include: (1) would interviewers and participants prefer using OpenEddi to other survey administration methods?; and (2) do the interviewers perceive demand for using OpenEddi in implementing research?

Implementation

"To what extent can a new idea, program, process, or measure be successfully delivered to intended participants in some defined, but not fully controlled, context?" Outcomes of interest for implementation in this study include: (1) can OpenEddi be used to collect data for a network study in rural Appalachia?; (2) are there any specific resources needed to implement OpenEddi in this setting?; and (3) what factors affect OpenEddi's implementation ease or difficulty?

Practicality

"To what extent can a new idea, program, process, or measure be carried out with intended participants using existing means, resources, and circumstances, and without outside intervention?" Outcomes of interest for practicality include: (1) was OpenEddi efficient in collecting data from participants?; (2) was the data collected using OpenEddi of good quality?; (3) were interviewers and participants able to use OpenEddi with ease?; and (4) did the use of using OpenEddi reveal any observed positive or negative effects on participants or interviewers?

Analysis

Qualitative data are reported directly from the author's notes and presented verbatim when possible. Descriptive statistics (eg, mean, SD, proportions) of ego data from the network study were analyzed using IBM SPSS Statistics Version 24 for Mac [49] and RStudio [50,51]. Network descriptives (size, number of edges, density, subnetwork proportions) were calculated using RStudio.

Results

Results are organized by the four feasibility focus areas, using both quantitative data from the network study and qualitative data from the group interview. Responses related to acceptability and demand were often provided in tandem. Similarly, issues of implementation and practicality overlapped. Therefore, we combined these responses into two groups to report results. In

addition to evaluating the practicality of OpenEddi, we included qualitative responses reflecting the practicality of the survey instrument administered in OpenEddi, and responses to the network visualization experience of OpenEddi.

Acceptability and Demand.

Qualitative group interview respondents reported that they enjoyed taking and administering the survey:

> *We absolutely loved using the tablet.*
>
> *Best survey I've ever done.*
>
> *People loved doing this survey.*
>
> *People were willing to do it and it was easy because it's just moving circles around.*

In addition, respondents reported that the survey was engaging, easy to use, and that they liked it better than other survey software they had previously used:

> *Our survey was engaging and they had to think about questions and not the same thing over and over.*
>
> *It's more engaging to think about friends and family than yourself. You have to think about the people you know.*
>
> *Other software is really challenging.*
>
> *School software is a lot more boring than this. It's all fill in the blank and strongly agree.*

Respondents reported that the bubble sorting of alters was fun:

> *It was fun like a video game!*
>
> *It was a lot more interesting and not the normal boring select one, and after three you want it to be over.*

However, the questions became repetitive, and interviewers suggested mixing up the structure and interchanging the bubble sort questions with standard multiple-choice questions:

> *Oh gosh another circle?*
>
> *People got tired of circles so if you could change up the structure that might be better. Mix it up.*

Interviewers stated that they wished they could use OpenEddi for all of their surveys. One interviewer expressed an understanding of how the software and network visualizations could be used in another intervention study she was involved in:

> *If we make people aware and spread information, it's beneficial to know who knows each other. For the FIT [fecal immunochemical testing] kits, if we had access to the survey networks we'd have access to these other people.*

There were usability issues in administering the survey to some participants with low or no literacy, including difficulty reading a smaller font size:

> *People who had never used an iPad either thought it was fun or they had a hard time. Even after increasing font size they couldn't read it. Younger people had an easier time than older.*
>
> *I had to read a lot of them.*

When qualitative group interview respondents were asked, "what would you change?" the responses were mostly aimed at: improving the visibility and literacy of the survey, including being able to choose a font size, color options, and shapes; having colors assigned to alter attributes (so that the bubble representing an alter would be a color that reflected an attribute assigned to that alter); and "anything to expedite the sorting!" One recommendation was to group alters by type of relationship before entering the pile sort exercise to make alter-alter tie connections easier, or to ask subsequent questions on a similar subgroup.

Implementation and Practicality.

Qualitative group interview responses related to implementation and practicality are reported first, followed by results from quantitative data collection.

Qualitative Group Interview Responses

The fact that an Internet connection was not needed to administer the survey was repeatedly brought up as a great benefit to using the survey software, but there were sometimes issues with syncing the data when an Internet connection was established. One respondent stated, "[Not needing Wi-Fi] not just made it easy, it made it *possible!* But there were some difficulties with syncing. " There were events of surveys not saving data after an entire survey was completed ("People had to re-do it. They were not happy *at all*.") and occasions when the survey would, "…kick you out and when you'd get back in, you could put the page number in the URL. I'd pay attention to what page it was on so in case something happened they could go back in and restart where they left off."

In relation to usability of specific features of OpenEddi, respondents reported that the pile sort was somewhat helpful, but hard to understand, and sometimes the software didn't work properly during this portion of the survey.

> *The rectangles [cards with alter names] gave you a head start…*
>
> *This was confusing, linking the squares on top of each other. Sometimes they wouldn't let you touch them.*

The interviewers made several suggestions for improving the pile sort:

> *Use the questions leading up to the pile sort to group people together so that you aren't starting from the beginning sorting people again.*
>
> *Make something where all the people in this column talk to all the people in that column. "Select all" for one column means everyone talks to one another.*

Similarly, issues arose with the graphic user interface of the nodelink diagram. One respondent mentioned the lack of distance in the graph, making the network difficult to visualize: "It was hard to see how it looked, like we're all together, because it pulled all the circles – so if it stayed further apart it would have been easier to see."

However, most responses were reflections on what the graph represented rather than the utility of the software. Respondents

were surprised at how densely connected their networks were, or at the size of their network:

> *Mine was a big group of people who were all connected and it was really close knit.*
>
> *Surprise. I'm surprised I talk to all of these people.*

Other respondents found that the visualization made them aware of what their network looked like, who was in it, and how it impacted her life:

> *It was a struggle to come up with a lot of people…the people I communicate with is really limited…*
>
> *My group is really small and I really need to branch out… if I was doing something for health or wellness I could see who I talk to for certain things...*

One interviewer mentioned that she had a participant who, after noticing that her network had a main core group and a couple people outside of it, realized that she was connecting two groups within her family that didn't communicate with one another. She stated, "I don't know why these people don't talk to other people because they talk to me." She was surprised by that. It was her family, and two people in the family who didn't talk to the rest and, "if it weren't for me they would never talk to each other," and she didn't realize it until she saw the diagram. "Maybe I should do something to make them talk to each other instead of relying on me to link them together."

One interviewer recommended using visualization, "to show the support they give you or show you who you talk to about certain things. I talk to these people about business things, and these about health." Other responses reflected the practicality of the survey that was administered via OpenEddi in this study. In response to the name generator question, "Name 25 people you know," respondents generally felt that 25 was, "a lot of people to come up with," it took a long time to name them all, and they were confused about who these 25 people should be. Interviewers reported having to ask participants to think of coworkers and other friends as people in their network because, "they only thought of kin." Respondents reported that after naming 25 people, participants really didn't want to add anyone else to the network.

Without prompting, the respondents reported their surprise at how few participants in the survey know the age and education level of those close to them: "These are their best friends and family and I don't know how old they are or level of education? How good friends we are and we don't know these little things?"

In addition, respondents reported participant reactions to multiple questions about trusting network members and others in the community.

> *People were really tore up about the who do you trust questions. They had close family members and friends and they would say that they only trust one person.*
>
> *Who trusts you? That would be hard to answer. They'd have an emotional break down and say, 'I DON'T KNOW!'*

One participant suggested that you could use your network graph to help select a person to trust who was less connected to the rest of their network, and would therefore be more likely to keep a secret: "You can look at your network! And pick that person way out there to tell something to!"

Quantitative Network Study Data

Our goal in the network study was to collect data from 160 women–40 initial participants (seeds) and up to 3 alters from each seed's network–and investigate whether referrals into the SCVS study flowed through women's health information networks or resource provision networks. We interviewed a total of 168 women, 71 (42.3%) of whom were initial seeds from the SCVS study, and 97 (57.7%) of whom were network members of those initial seeds. The nurse interviewers found that recruiting the network members was more challenging than the initial seeds, although the proportion of initial seeds to alters recruited varied by interviewer.

There were technical issues with syncing the data when a Wi-Fi connection was established, and in saving the data locally. This first instance of OpenEddi used in the field (Version 0.2) was built on third party libraries for Application Program Interfaces (APIs) and database management to hasten the implementation of the software in the field. When the bugs inevitably emerged that affected the storage and retrieval of data, it became very difficult to locate and resolve the issues, and a portion of the collected data was lost.

In our final dataset, we have data from 84 egos (50.0% of 168 interviews), with data on 1750 alters, and 8698 ties between alters. However, due to the nature of the data loss, we can only link 53 egos (39% of total interviews) to their alters and alter ties in the dataset, giving us only 53 complete networks. Furthermore, we lost the identification data that we needed to link the initial seeds to the participants, so we were unable to distinguish which of the 53 egos were initial seeds and which were network members recruited from those seeds. Finally, of those 53 egos for whom we have complete network data, only 33 have complete ego data, meaning that for 20 of the 53 egos we have data on their alters and the ties between alters, but their individual-level survey data is among the lost data. This problem greatly limited the analyses we could conduct and the conclusions that can be drawn from the quantitative data.

We can use data from 84 egos to explore nonnetwork inquiries. Of the 84 egos, 50 (60%) had participated in the SCVS study. We had planned on linking our data from women who had participated in the SCVS study to the SCVS study data, so we only have sociodemographic information from the 34 women (40%) who *did not* participate in the SCVS study (shown in Table 1); most were non-Hispanic (99%), white (100%), had less than US $1000 per month in income (60%), and had children (73%). These results are representative of the population of the KRADD, which is 97.2% white and 0.6% Hispanic, and the median annual household income is US $28,022.

Table 1. Characteristics of network study participants, n=84 unless otherwise noted.

Variable	n (%)
Use the Internet or email at all (n=79)	67 (80)
Frequency of Internet or email use (n=67)	
Daily use	41 (61)
Weekly use	23 (34)
Less often	3 (4)
Devices used to access the Internet (n=67)	
Desktop computer	32 (48)
Laptop computer	44 (66)
Mobile phone or smartphone	56 (84)
Tablet computer	30 (45)
Participated in SCVS study	50 (60)
Demographic characteristics of network study participants who did not participate in the SCVS study, n=34	
Age, mean (SD)	36.9 (14.1)
Race white (n=34)	34 (100)
Hispanic ethnicity (n=30)	1 (1)
Monthly income (n=30)	
Less than US $1000	18 (60)
US $1000 to $2000	9 (30)
More than US $2000	3 (1)
Have children (n=30)	22 (73)
Have children under age 18 living in home (n=29)	16 (55)
Structural characteristics of networks, n=53	
Size, mean (SD)	12.6 (8.8)
Density, mean (SD)	0.67 (0.32)
Proportion of networks with density = 1	23 (43)

We can use data from the 53 complete networks to look at structural network characteristics (ie, size, number of edges, and density) and data on the alters and alter ties that exist in those 53 networks (see Table 1). Network size ranged from 2 to 27, with a mean of 12.6 alters. Network density, or the proportion of ties between alters present out of all possible ties between alters, ranged from 0.13 to 1. A network density of 1 results when every alter is connected to every other alter, which was observed in 43% of the networks in this study. In this study, ties between alters were defined loosely by the question, “Can you tell me which of the people on that list talk to one another?“

Figure 4 shows a sample of 8 participant networks, chosen at random. The circles are nodes, which represent network members. The grey lines are ties between network members. The ego is not included in the network diagram. In this figure, colors reflect the category of relationship the ego indicated for each alter. Most of these networks (5/8) show a single connected component, but three of them have two components, demonstrating that the ego has two groups of people in their network who do not interact with each other.

In the survey, we asked women with whom in their network they talk about health topics such as HPV, the self-collected vaginal swab, and cancer, and also with whom they talk about where to get things they need for the best price (a proxy for market mavenism). Figure 5 displays a sample of 8 participant networks with the white nodes representing alters with whom the ego reported talking with about any of the above topics. Darker lines indicate a tie between two of these alters. As demonstrated, some egos didn’t talk to any of their alters about these topics, and some talked to all of their alters. The proportion of the network with whom they communicated about these topics varied across egos. Further analyses will explore these subnetworks in-depth.

Figure 4. A random sample of 8 participant networks with node color representing type of relationship reported for each alter.

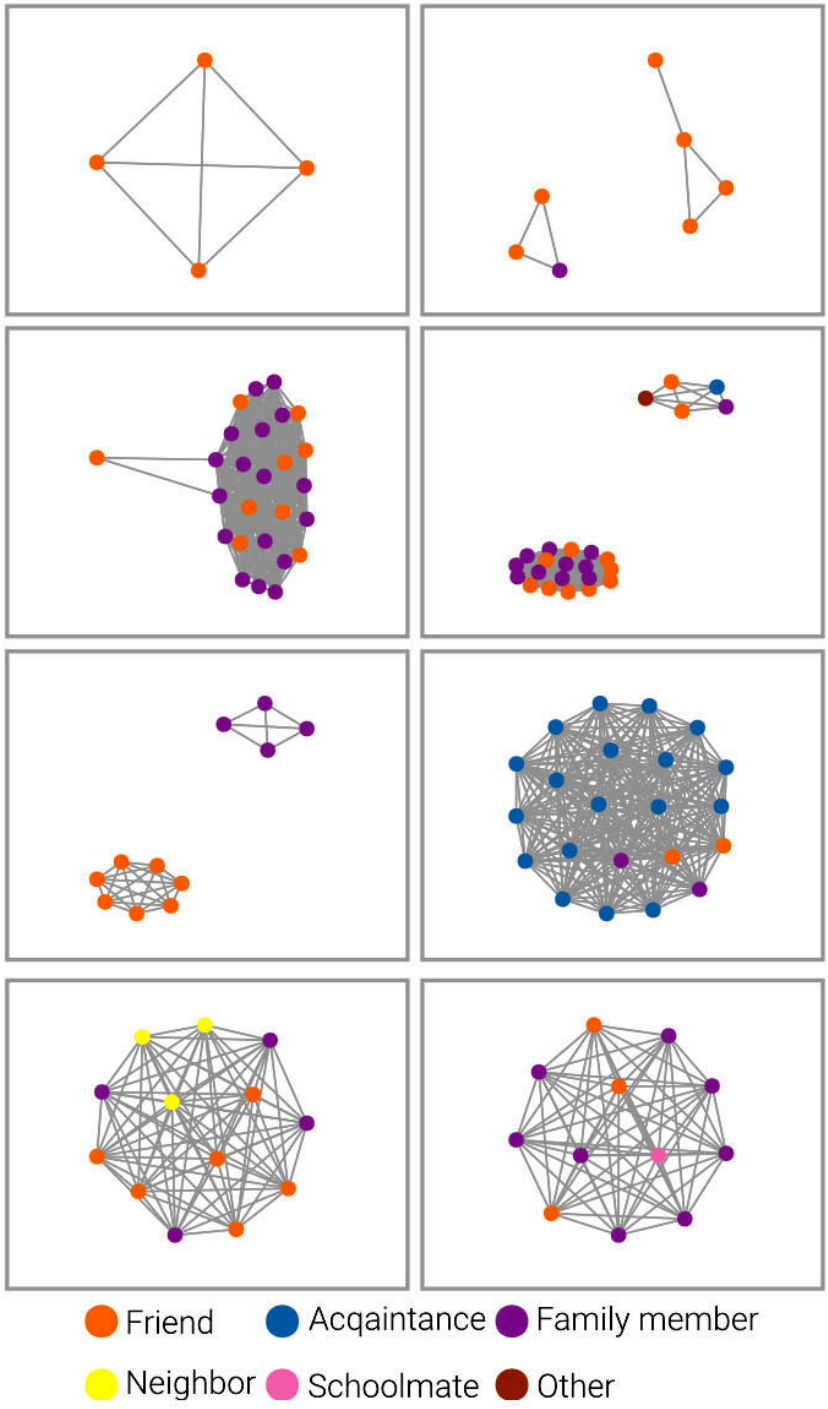
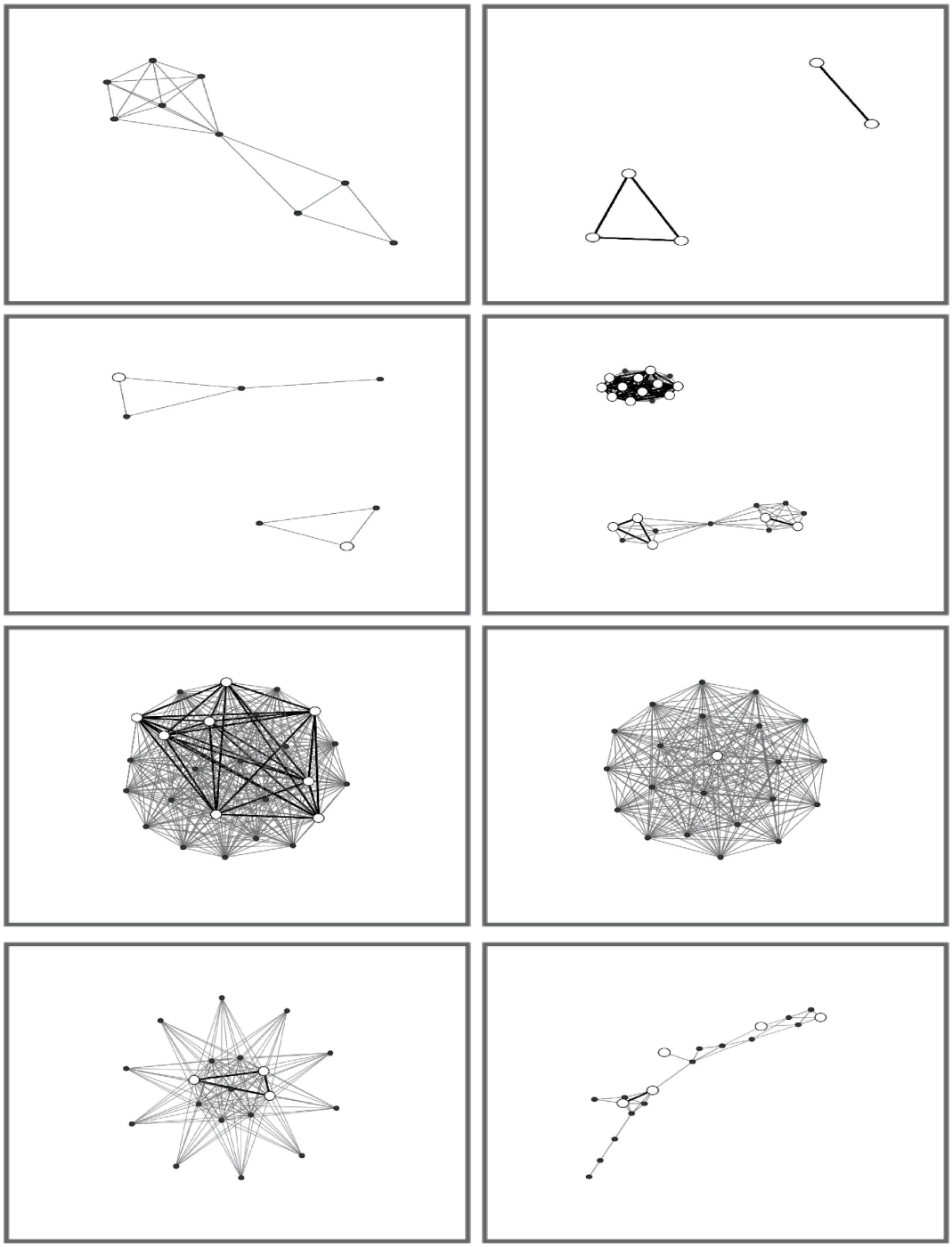


Figure 5. A sample of 8 participant networks with white nodes indicating alters with whom the ego talks about certain topics.



Discussion

The purpose of this paper is to report on the early-stage feasibility of the OpenEddi data collection tool in a rural Appalachian population. In a qualitative group interview of a limited number of users, we found that OpenEddi was well received, useful, didn't feel burdensome, and was fun to use. However, technical issues hindered the implementation of OpenEddi, and areas were identified for improved practicality of the tool for lower literacy users.

Due to the amount and type of data lost, we were unable to investigate our initial hypothesis about the type of network women accessed to recruit others into the SCVS study. It has yet to be determined what conclusions, if any, we may draw from the network study's remaining data. We plan to analyze and present detailed survey data from the 84 egos in a separate paper, as well as the complete network and survey data of 33 egos. The descriptive data of the personal networks of rural Appalachian women, and the rich data we collected from egos on topics such as health communication sources and networks, health care access, social capital, political engagement, and use of an innovative screening method for HPV, will still fill an

existing gap in the literature on networks of rural Appalachian women.

To address the technical issues that led to data loss, we have completely rebuilt the OpenEddi data collection platform in a more reliable way. The software has been rebuilt from the ground up using a more appropriate set of tools for storing and retrieving data: NodeJS, a custom API built using Express 4; and a PostgreSQL database, which made wide use of the JavaScript Object Notation data type. Not only is this new version (Version 0.3) easier to debug, it also better suits the adaptable vision of the software.

Most of the time, we were successfully able to collect data in people's homes and places of employment (even at a Dairy Queen), without an Internet connection, in a rural and geographically isolated area of the United States. The nurse interviewers felt that we would simply have been unable to conduct the study if an Internet connection had been required. Collecting data at a designated office, or in the homes of people who had a computer with an Internet connection, would have severely limited the diversity of socioeconomic status, technology use, and geographic location of our study sample. Having a mobile data collection tool allowed the interviewers to survey participants wherever they were, which not only broadened the reach and representativeness of the sample but also sent a message to underrepresented and understudied participants that we, as researchers, value their time and their perspectives.

We did not formally assess respondent and interviewer fatigue or completion time in this study. However, the nurse interviewers using OpenEddi greatly appreciated that they did not have to enter the data from paper-and-pen surveys, and even when the technology failed, they felt it was less burdensome than other surveys they had administered. Of note, none of the interviewers had ever administered a network survey, yet they still preferred the network survey to any standard survey they had previously administered. Respondents reported that participants in the network study were excited to use the tool, regardless of familiarity with technology, and found it to be fun, like a game. There was a learning curve for some participants unfamiliar with touch-screen technology, but more barriers were raised in response to basic literacy needs such as changeable font size, shape and color of nodes, and text-to-speech options.

Our research team has identified these issues of literacy as a primary area of focus for the development of OpenEddi. Respondents believed that a text-to-speech option would be beneficial, but insisted that it be an option in the software for each question, not that the entire survey be delivered only via audio. We recommend interviewer-guided data collection in populations with potentially low literacy to assist participants with understanding and navigating software, to provide a more personal experience, and to be able to identify struggles with literacy and compassionately help participants engage in the research.

Respondents in our study found the visual-based bubble sorting procedure and nodelink diagrams to be fun and easy to understand. The pile sort, in contrast, was difficult for participants to use without explicit guidance. The pile sort procedure may not have matched the way participants cognitively stored relationships between network members, or the layout of the task on the screen may have been too complex. We have designed additional methods for collecting alter-alter tie data, and plan to design and test additional approaches to structuring survey questions among populations with varying levels of literacy. By using nonlinguistic graphics and creating visual representations of common response scales we may better reach low-literacy users while enhancing the experience for all users.

The participants in this qualitative group interview had excellent suggestions for reducing the burden on survey users by expediting sorting of (or characterizing) alters and identifying alter-alter ties. We now offer four different methods of eliciting alter-alter ties in OpenEddi: (1) the pile sort; (2) the nodelink diagram; (3) the box pop, which is a unique variation on the traditional pair list (listing every pair of alters and asking if they have a tie); and (4) an alter grouping method in which alters can be assigned to groups of people who are all linked based on some attribute (eg, family, coworkers, attended an event). Any of these approaches can be used as a method on its own to identify alter-alter ties. If visualizing the network is a goal of the data collection process, any of these approaches may be used to first elicit alter-alter ties, then the ties can be visualized as a nodelink diagram. Alternatively, the nodelink diagram can be used alone to both elicit and visualize the alter-alter ties.

In a randomized trial comparing the first three of these OpenEddi methods (the alter grouping wasn't yet fully developed) with two established computer-based alter-alter tie methods (pair list and matrix) and two paper-and-pen methods (paper matrix and paper nodelink), we found that these methods yielded significantly different results on some measures (unpublished data). However, the OpenEddi nodelink diagram stood out as the favorite, scoring highest on all user satisfaction measures. Finally, we have changed the springiness of the force-directed graph in the nodelink diagram, which may reduce crowdedness and improve participants' ability to visualize and comprehend their networks.

Perhaps the greatest discovery in this informal feedback session was the impact of visualizing network structures on the participant. Participants reported understanding their own networks better and seeing how links (or absence of links) impacted their lives. The respondent who was surprised at how small her network was and that she didn't trust many people felt that this information allowed her to see where she could make changes to improve her social support network. Another respondent saw how she could leverage her network structure for a specific opportunity. She identified an isolate in her network ("that person way out there") as the person to talk to about an issue she wanted kept secret, because she saw that node wasn't connected to anyone else in her network. Upon the realization that she was the only person linking two disconnected factions of her family, one participant felt that she shouldn't be the only "go-between" and that she needed to stop playing that stressful role.

Although we did not design the study to make use of the responses that the network graph might produce in participants, this approach presents opportunities to empower women from a resource-poor community to make changes in their own social networks. Using personal network visualization and feedback, we can tailor interventions to individuals by identifying areas of need and connecting them to new resources and information, tools for building social support, or other strategies for maximizing the positive support and resources available in their network [11,52-55].

There are exciting projects ongoing in the field using this approach, such as using motivational interviewing (MI) with network visualization to reduce risk behaviors among persons transitioning from homelessness to stable housing [56]. In this intervention, for instance, an individual can see clearly through network visualization who in their network uses or encourages use of substances, and the interventionist can use MI to help the individual work through strategies to disconnect from those network members, or create stronger ties between network members who positively support the individual. In addition, Kennedy et al found that network visualizations can be used in populations with less than high school levels of education [53,57]. Dhand et al [14] are using the personal network characteristics of neurological patients to understand how network ties impact stroke outcomes, and propose additional research building clinical, evidence-based network interventions for neurological patients. We are developing a clinical network intervention for cancer patients, survivors, and caregivers to improve social support and resource provision over treatment and survivorship.

Based on the qualitative group interview data, we don't know whether the reflections of the respondents on their network structures led to any network changes, but they do indicate that there is potential for this type of intervention. In our study, if the interviewer had been trained in MI, she could have helped the participant who no longer wanted to serve as the only link between family factions develop specific strategies to do so, by building self-efficacy to make that network change. On a population level, network visualization can potentially increase the social capital of a community by enabling individuals to see, understand, and leverage resources and support in their networks that they may otherwise be unaware of. Interventions using community-based network models (like lay health workers and change agents) have great potential for success in Appalachia [42]. For those researchers interested in reaching marginalized populations with resources and skills to improve their opportunities to be healthy, we hope to couple these community-based interventions with more tailored network feedback to individuals by arming community health workers with interactive network visualization software and training in MI. Future research should investigate this possibility.

Limitations

This is the first study evaluating the use of a mobile network data collection and visualization tool in a rural Appalachian population, but there are several limitations. The qualitative study reported in this paper is limited by a very small sample size of only six individuals. Although this group captures 100% of the interviewers involved in the network study, the two network study participants only represent 1% of our total network study sample, including those whose data were lost. We appreciated that the interviewers could relay the experiences and comments of the participants they interacted with in administering the survey. In addition, the two women who did participate were known acquaintances of the interviewers, who agreed to volunteer their time, which represents a convenience sample. We used this approach because our original intent was to gain informal feedback to inform our continued development of the software, not to share the results. This issue limits the generalizability of our findings, and drives us to conduct additional research to further investigate the feasibility of OpenEddi.

In addition, the qualitative group interview took place nearly eight months after completion of data collection in the network study. The participants in our group interview were relying on their memory of the software and survey experience. This issue limits our ability to evaluate some of the nuances of using the software, but participants remembered their individual experiences with the software even after an extended period of time; some with very compelling stories of the impact of network visualization on their perception of their networks. Our next assessments of OpenEddi feasibility in the field will include a formal structure for recruitment, implementation, and qualitative data analysis. In addition, we are incorporating iterative usability testing and evaluation of the software as we continue to develop OpenEddi.

Conclusion

This paper presents observations on the feasibility of using a touch-screen, tablet-based network data collection tool in a predominantly low-income, low-education population of rural Appalachian women. Qualitative feedback and implementation data have shown us that our tool, OpenEddi, has the potential to be successfully used in this population, yet there are improvements that must be made to further enhance the network science experiences of this group. Our next steps are to incorporate the feedback provided into the survey tool. We have rebuilt the OpenEddi software platform and are currently creating and testing new methods of question display. We have developed and tested several new methods of obtaining ties between alters (unpublished data). As we develop and test these methods, we will evaluate the quality, efficiency, and acceptability of these new mechanisms in comparison to existing network data collection methods.

Specifically, we plan to directly compare multiple data collection methods by implementing an identical full survey via OpenEddi, at least one established computer-based network data collection method, and at least one established paper-based method. We hypothesize that among higher-literacy users, data quality will be similar across methods, but that satisfaction and efficiency will be highest among the OpenEddi users. Among low-literacy users, we hypothesize that data quality, satisfaction, and efficiency will be highest among the OpenEddi users. By using playful design, we hope that a more enjoyable survey experience will lead to participants committing to survey completion and engaging in the survey process again for longitudinal studies,

resulting in more accurate and reliable network data and attitudes towards engaging in network research.

The ability for existing scales and measures to be adapted to a visual representation while retaining validity and reliability is promising (eg, iPadVAS [58]). We will continue to develop and test visual-based question types and modules created specifically for acceptability and use in low literacy populations.

A tool like OpenEddi can enhance community-based research in areas such as rural Appalachia by reaching underserved populations with effective information and connecting them to health and social services. Finally, we will continue to develop specific applications of the OpenEddi data collection and visualization tool in community-based and clinical settings for evaluating and intervening with social support and communication networks.

Acknowledgments

This work was supported (in part) by a Building Interdisciplinary Research Careers in Women's Health grant (#K12 DA035150) from the Office of Women's Health Research and National Institute on Drug Abuse, and by the RCPC, a Centers for Disease Control and Prevention and Department of Health and Human Services Prevention Research Center (1U48DP001932).

Conflicts of Interest

Katherine Eddens and Jesse Fagan have an ownership interest in Flaming Fox, LLC, which produces the open-source software OpenEddi.

Multimedia Appendix 1

Description of OpenEddi design and network survey, with examples and screenshots of the OpenEddi survey.

[PDF File (Adobe PDF File), 1MB - resprot_v6i6e124_app1.pdf]

Multimedia Appendix 2

Video demonstration of sample network data collection features of OpenEddi Version 0.3 (rebuilt version).

[MOV File, 84MB - resprot_v6i6e124_app2.mov]

Multimedia Appendix 3

Additional features or question types of OpenEddi Version 0.2 that are currently being incorporated into Version 0.3: a) The bullseye feature represents closeness of alters to the ego; b) and c) demonstrate additional ability to answer questions by ego or by using a predetermined roster of names; d) network members or alters named in response to a specific question (eg, "With whom did you talk about the HPV self-swab study?") are brought up for recruitment into the study, to ease the ability to contact network members for snowball sampling or respondent-driven sampling.

[PNG File, 728KB - resprot_v6i6e124_app3.png]

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Abbreviations

API: Application Program Interface
HPV: human papillomavirus
IRB: Institutional Review Board
KRADD: Kentucky River Area Development District
MI: motivational interviewing
RCPC: Rural Cancer Prevention Center
SCVS: self-collected vaginal swab
SD: standard deviation

Edited by M Focsa; submitted 01.11.16; peer-reviewed by JH Lee, S McIntosh; comments to author 15.11.16; revised version received 23.04.17; accepted 29.05.17; published 22.06.17.

Please cite as:
Eddens KS, Fagan JM, Collins T
An Interactive, Mobile-Based Tool for Personal Social Network Data Collection and Visualization Among a Geographically Isolated and Socioeconomically Disadvantaged Population: Early-Stage Feasibility Study With Qualitative User Feedback
JMIR Res Protoc 2017;6(6):e124
URL: http://www.researchprotocols.org/2017/6/e124/
doi:10.2196/resprot.6927
PMID:28642217

Original Paper

Reducing Parental Uncertainty Around Childhood Cancer: Implementation Decisions and Design Trade-Offs in Developing an Electronic Health Record-Linked Mobile App

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Abstract

Background: Parents of children newly diagnosed with cancer are confronted with multiple stressors that place them at risk for significant psychological distress. One strategy that has been shown to help reduce uncertainty is the provision of basic information; however, families of newly diagnosed cancer patients are often bombarded with educational material. Technology has the potential to help families manage their informational needs and move towards normalization.

Objective: The aim of this study was to create a mobile app that pulls together data from both the electronic health record (EHR) and vetted external information resources to provide tailored information to parents of newly diagnosed children as one method to reduce the uncertainty around their child's illness. This app was developed to be used by families in a National Institutes of Health (NIH)-funded randomized controlled trial (RCT) aimed at decreasing uncertainty and the subsequent psychological distress.

Methods: A 2-phase qualitative study was conducted to elicit the features and content of the mobile app based on the needs and experience of parents of children newly diagnosed with cancer and their providers. Example functions include the ability to view laboratory results, look up appointments, and to access educational material. Educational material was obtained from databases maintained by the National Cancer Institute (NCI) as well as from groups like the Children's Oncology Group (COG) and care teams within Cincinnati Children's Hospital Medical Center (CCHMC). The use of EHR-based Web services was explored to allow data like laboratory results to be retrieved in real-time.

Results: The ethnographic design process resulted in a framework that divided the content of the mobile app into the following 4 sections: (1) information about the patient's current treatment and other data from the EHR; (2) educational background material; (3) a calendar to view upcoming appointments at their medical center; and (4) a section where participants in the RCT document the study data. Integration with the NCI databases was straightforward; however, accessing the EHR Web services posed a challenge, though the roadblocks were not technical in nature. The lack of a formal, end-to-end institutional process for requesting Web service access and a mechanism to shepherd the request through all stages of implementation proved to be the biggest barrier.

Conclusions: We successfully deployed a mobile app with a custom user interface that can integrate with the EHR to retrieve laboratory results and appointment information using vendor-provided Web services. Developers should expect to face hurdles

when integrating with the EHR, but many of them can be addressed with frequent communication and thorough documentation. Executive sponsorship is also a key factor for success.

Trial Registration: ClinicalTrials.gov NCT02505165; https://clinicaltrials.gov/ct2/show/NCT02505165 (Archived by WebCite at http://www.Webcitation.org/6r9ZSUgoT)

(JMIR Res Protoc 2017;6(6):e122) doi:10.2196/resprot.7523

KEYWORDS

electronic health records; mobile apps; uncertainty; ethnographic design

Introduction

Parents of children newly diagnosed with cancer are confronted with multiple stressors that place them at risk for significant psychological distress. In a short span of time, they are expected to become familiar with medical terminology, learn and understand treatment protocols, manage complicated medication regimens and support their child through the associated side effects, communicate with their child's care team, and attend numerous testing and medical appointments. Parents must do all of this while advocating and providing emotional support for their child as well as continue to manage the ongoing responsibilities of home, career, and in many cases, their other children [1]. For many parents, the sudden and intensive demands generate feelings of uncertainty and can lead to symptoms of anxiety and depression, impaired cognition, and disrupted sleep [2,3]. Not surprisingly, parental distress can negatively impact a child's well-being as well. Therefore, addressing the needs of parents is important for the health and well-being of both parent and child during this difficult peri-diagnostic period [1,4-6].

One strategy that has been shown to reduce uncertainty is the provision of basic information [7]; however, families of newly diagnosed cancer patients are often bombarded with educational material. At the time of diagnosis, well-meaning medical teams typically provide every family with a large binder that contains hundreds of pages of paper documentation. Given to the family all at once, much of the binder content may not be applicable to their child and is often only relevant during a particular phase of treatment. For a number of parents, the binder, provided with the intent to decrease uncertainty, may have the opposite effect. Still other parents may avoid the binder altogether and never open it. In contrast, technology has the potential to help families manage their informational needs and move towards normalization of their lives [8]. As the "5 Rights" framework, established for decision support, seeks to deliver the right information to the right person(s), using the right format, in the right channel, at the right point in the workflow [9], the same 5 rights can be applied in helping deliver the most relevant information to families of children with cancer at the proper time.

We sought to create a mobile app that pulls together information from both the electronic health record (EHR) and external and vetted information resources, in order to provide tailored information to parents of newly diagnosed children as one method to reduce the uncertainty around their child's illness. To develop an optimal app interface, an interdisciplinary team conducted a user-centered design process to define and prioritize the content and features. The application was developed to be used by families in a National Institutes of Health (NIH)-funded randomized controlled trial (RCT) aimed at decreasing uncertainty and the subsequent psychological distress. This RCT is currently underway and recruiting at Cincinnati Children's Hospital Medical Center (CCHMC) and the University of Oklahoma Health Sciences Center (OUHSC). This paper describes the implementation decisions that occurred in translating the output of the design process into a functioning mobile app along with best practices and recommendations for others embarking upon similar projects.

Methods

Trial Design

The proposed trial seeks to recruit up to 300 participants over a 3-year period, with an additional year for follow-up and analysis. Participants are recruited from patients at CCHMC or OUHSC who are under the age of 18 and who are newly diagnosed with leukemia, lymphoma, or a malignant tumor (2 to 12 weeks post diagnosis). The parents of the patients are also recruited. Participants are randomized into one of the following 2 interventions: (1) Illness Management and Parental Adjustment to Cancer Treatment (IMPACT), or (2) education and support only (ESO), which serves as the control. Parents receiving the IMPACT intervention will participate in 6 sessions where they receive feedback on ways to manage their uncertainty, with the first 3 sessions focused on uncertainty prevention and the last 3 on responses for situations in which uncertainty cannot be prevented or avoided. In addition, parents have access to the mobile app, which will increase their access to knowledge about their child's illness and treatments. Those in the ESO (control) group will participate in 6 sessions, where they will receive general support as well as education on cancer etiology, medical treatments, potential short- and long-term effects of treatment, and other resources that are often helpful to parents of children with cancer. The hypothesis is that IMPACT will teach parents about uncertainty prevention and management through the use of medically-specific communication, information management, and problem-solving skills. Parents and children are expected to complete online measurements at baseline and the 1-week and 3-, 6- and 12-month follow-up appointments. The primary outcome measure is psychosocial functioning as assessed by the Global Severity Index of Symptom Checklist-90-Revised [10]. The secondary outcome measure is the post-traumatic stress symptoms score as assessed by the Impact of Events Scale-Revised [11]. Potential mediators of the treatment effects, including levels of uncertainty and use of the mobile app, will also be examined.

Ethnographic Design Process

A 2-phase qualitative study was conducted to elicit the features and content of the mobile app based on the needs and experience of parents of children newly diagnosed with cancer and their providers [12]. The first phase consisted of semi-structured interviews with children with cancer and their parents. In the second phase, caregivers and healthcare providers were asked to identify and rank a series of app functions that were derived from the results of the interviews in phase 1. Example functions include the ability to view laboratory results, look up appointments, and to quickly access educational material through a search function. The output of this second phase was then converted into a series of wireframes. These prototypes were tested for their ease of navigation and aesthetic before being turned into a final design. For a full description of this process see Morrison et al [12].

Technology Platform

The app was developed to run on iOS and Android operating systems, and targeted to tablet and phone form factors, though it will also run on a desktop or laptop computer. Due to resource and timing constraints, a decision was made to create a responsive Web-based app that functions similarly to a native app and scales content based on the size of the device's screen. The app was developed using the Java Enterprise Edition (EE) version 7 stack. The app front-end was created using Cascading Style Sheets (CSS) version 3 and Hypertext Markup Language (HTML) version 5.

Integration With External Sources

A key requirement that emerged from the design process was the ability to access information from the patient's EHR in as close to real-time as possible. CCHMC's EHR vendor is Epic (Epic Systems, United States). Oklahoma is transitioning vendors. Many EHR vendors, including Epic, now offer Web services that can be used to retrieve production data, providing an opportunity for real-time access. As the primary users of this app are patients and families, we focused on those Web services that support Epic's personal health record, MyChart. Doing so allows us to leverage MyChart's authentication and authorization protocols, which means parents and families can sign on with their MyChart username and password, obviating the need for a second set of credentials. Our primary Web services of interest were those relating to the retrieval of laboratory results and appointment information.

Content on medical terms and the list of medication names were obtained from databases maintained by the National Cancer Institute's (NCI) Dictionary of Cancer Terms and Drug Dictionary, respectively. The NCI Drug Dictionary was used to retrieve more medication information from services that query Medline Plus, which is run by the National Library of Medicine (NLM). Additional educational materials were obtained from the Children's Oncology Group (COG) and care teams within the CCHMC's Cancer and Blood Diseases Institute. These electronic documents reflect much of the same content from the traditional paper binders that are given to families. Links to disease specific information were also incorporated as resources along with information on health promotion and disease prevention.

Results

The ethnographic design process resulted in a framework that divided the content of the mobile app into 4 sections: (1) Journey, which conveys information about the patient's current treatment and other data from the EHR; (2) Education, where users can find background material and additional medical information; (3) Calendar, which allows users to view upcoming appointments at the medical center or other items that they have added; and (4) Study, the section where participants in the RCT document the study data. The content of each section is detailed in Table 1, along with the expected source of that information. The content of the "Study" tab is not shown as the intervention is still ongoing. Example screens from the application are shown in Figure 1.

Table 1. Functionality of the mobile app by section and the expected source of information for each component.

Section	Feature	Description	Source of information
Journey	Results	Provides a list of the patient's laboratory results and the ability to drill into individual results	EHR[a]
	Medications	A list of the patient's current medications	User-generated from lists sourced from the NCI[b] Drug Dictionary and Medline Plus[c]
	Care team	Information on members of the patient's care team (eg, picture, title, contact information, specialty, etc)	User adds team members using text auto-complete; information pulled from hospital systems
	Notes	Any text notes that the family wishes to document	User-generated
Education	Lifestyle	Background material on topics such as health and wellness, nutrition, and school and learning	Educational handouts from CCHMC[d] and the COG[e]
	Terms	A list of common medical terms and their definitions	NCI[f] Cancer Terms database
	Procedures	Descriptions of common procedures used in the treatment of cancer, information on transfusions, and on how to interpret laboratory results	Educational handouts
	Treatments	Background information on the treatment process and other ancillary information related to the care process	Organizational handouts from CCHMC and the COG
Calendar	Upcoming	A description of the patient's next appointment at the medical center, (including location and date/time) or other event entered by the user	EHR or user-generated
	Month view	Monthly view of appointments pulled from the EHR or manually added by the user	EHR or user-generated

[a]EHR: electronic health record (MyChart Web service).

[b]NCI: National Cancer Institute.

[c]While it is possible to retrieve these data via Web services, there were concerns about the accuracy of this information.

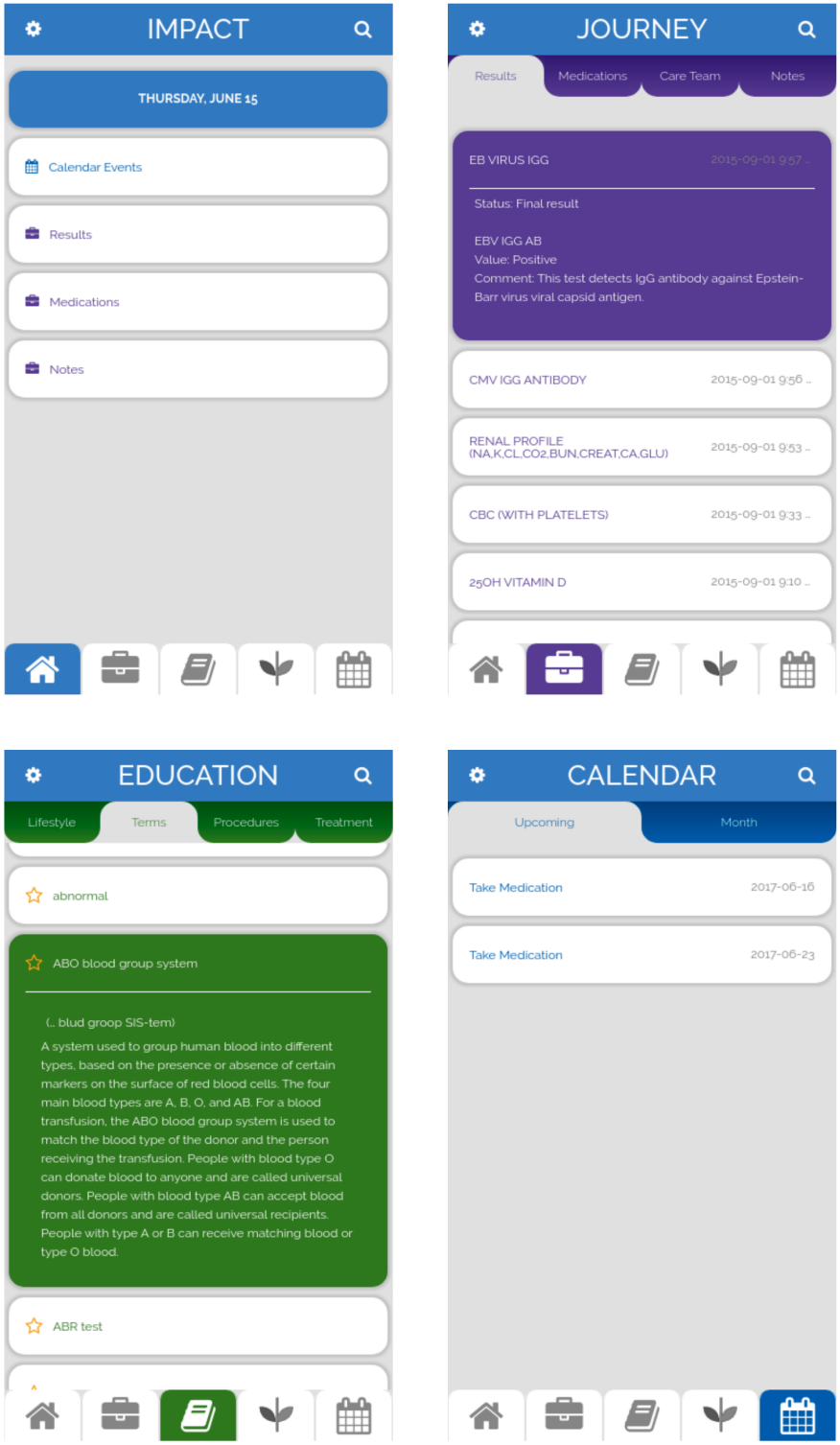
[d]CCHMC: Cincinnati Children's Hospital Medical Center.

[e]COG: Children's Oncology Group.

[f]NCI: National Cancer Institute.

At the time of final submission (June 2017), the app was being used by 63 participants (patient or family) across the 2 trial sites. There have been approximately 1970 logins since it was deployed, with iOS and Android devices accounting for roughly 75% (66/81) of all device activity (some users log in on multiple devices). As the trial is ongoing, we do not yet have results on the utility of the app. The app is used with families during each IMPACT intervention session, which provides an opportunity to test functionality on a regular basis. Families are also asked to report any problems that occur during their use of the app. These issues are addressed in real-time during the IMPACT sessions. App content, including links to, and content from, external sources, will be reviewed and updated on a yearly basis. We will also monitor usage of the app through Google Analytics, and participants will also be asked for feedback on ease of use, navigation, and overall satisfaction.

Figure 1. Screenshots of the mobile app. Examples of the home screen (top left), and content from the Journey (top right), Education (bottom left), and Calendar (bottom right) sections. The lab results in the Journey section are simulated. The Study tab is not shown, as the intervention is ongoing.



Design Trade-Offs

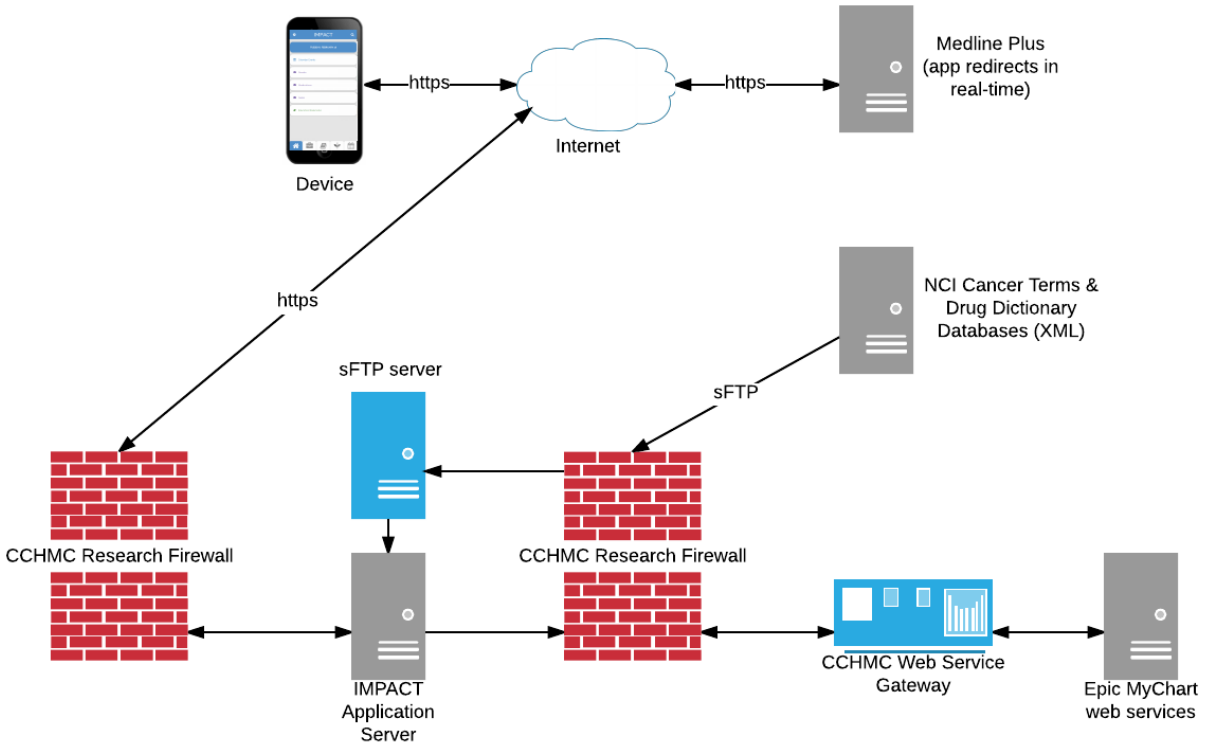
Informatics staff participated in the ethnographic design process and provided feedback about the feasibility of implementing certain features during the pilot period. This helped ensure that the expectations of the design participants were aligned with what could be delivered given the project budget and development timeline. Examples of features that were removed

before the design was finalized included the ability to use the app to chat with or send messages to the care team, to allow provider input of personalized treatment protocols, and real-time notifications about new or updated laboratory results. The app provides the ability for users to quickly find material based on their needs. Information on medications or medical terms is indexed and easily searchable, as are the educational modules, which have been developed to provide guidance on situations faced by families dealing pediatric cancer (eg, returning to school, dealing with siblings). Our original intention was to provide tailored material to each patient/family, but we found that it was not possible to develop individual protocols by treatment course at each stage of treatment within the project timeline. This work is currently underway as part of a separate project, and our intent is to integrate the material in a future version of the app. As an alternative, based on patient and family feedback, we have provided links to trusted sources where some of this information can be found (ie, NCI and COG).

Integration With External Sources

Content from the NCI Dictionary of Cancer Terms and Drug Dictionary were retrieved as Extensible Markup Language (XML) files and staged on the IMPACT app server. A public application program interface (API) that would have allowed us to retrieve this information in real-time was not available at the time of our implementation. The NCI supports a widget that would allow the dictionary to be embedded in a website, but this functionality did not meet our design needs. Following a process recommended by the NCI staff that maintained these databases, we retrieved the content as a series of XML files over the secure File Transfer Protocol (sFTP). We could receive notifications if updates were made to these databases, which would provide an opportunity to download a new version. Integration with the services provided by the NLM was straightforward. Medline Plus is configured to support responsive design and requests were redirected from the app. The material that was sourced from the traditional educational binders was more difficult to incorporate into a seamless mobile experience. Much of this content was directly converted from a text-heavy, paper-handout format, which is difficult to read on a mobile device. A diagram that illustrates the app infrastructure is shown in Figure 2. All traffic to external websites (eg, Medline Plus) is handled as redirects on the user's device. All data are encrypted in transit via Secure Sockets Layer (SSL) encryption. The app database is currently being migrated so that the data are also encrypted at rest.

Figure 2. Diagram of the app infrastructure. Calls to Medline Plus are redirected in real-time. Content from the National Cancer Institute (NCI) is staged on the Illness Management and Parental Adjustment to Cancer Treatment (IMPACT) app server. Requests to the Epic Web services are brokered through the Cincinnati Children's Hospital Medical Center (CCHMC) Web service gateway.



Because the Oklahoma site was transitioning EHRs, our integration efforts were focused on the CCHMC EHR. For non-CCHMC users, screens were created within the administrative interface of the app to allow coordinators to enter data manually. Accessing and retrieving data from the CCHMC EHR Web services was successful, but presented several hurdles. The lack of a formal institutional process for requesting Web service access, with documentation of all of the steps needed to for completion proved to be the biggest barrier. This was compounded by the fact that we had difficulty in identifying the most appropriate Web services to use in order to obtain the data in question. Documentation on available services was sparse, making it a challenge to figure out which service was the most appropriate. Finally, in our institution's development

and testing environments, Web services were configured to point at different instances of the EHR. Some services would return old production data, while others would return dummy results. After our project was completed, this was eventually resolved by creating a process that ensured that each time a Web service was activated, it was activated in all environments.

Discussion

Lessons Learned

Applying the process of ethnographic design resulted in a specification that can meet the needs of prospective users. Having informatics staff engage in the design process itself can provide benefits as decisions are made on how to translate specifications into an actual product. Trade-offs are often necessary, whether due to budgetary or time constraints, technology limitations, or other factors. Identifying potential challenges early allows information and possible solutions to be factored into the final result or future iterations. For example, the ability for families to interact with their care team through the app was identified as a high priority feature, but we did not want to create a channel that would direct communication to a clinician's personal mobile device. MyChart services exist that allow external apps like the one we created to utilize "official" communication channels. We ultimately decided that the inclusion of messaging in an initial release would introduce unnecessary complexity, but we were able to outline how the process might work in the future. Real-time notification of new or updated laboratory results is another example of a desired feature that was ultimately removed from the final design. In this case, no default service exists that would trigger an external alert that new or updated information was available. This functionality could be approximated by periodically polling the result services for updates, but we were concerned about the potential stress that this might put on the production EHR, so this feature was also deferred.

To successfully obtain data from the EHR via Web services, we had to overcome a number of hurdles, but these proved to be primarily due to institutional, social, and cultural issues. The lack of a formal process for requesting access to the EHR Web services and ensuring that the request, once approved, would be completed, proved to be the single biggest bottleneck. There were various institutional channels for socializing the project and receiving executive approval, but ensuring that this approval translated into action at the staff level was more difficult. At CCHMC, informatics is a separate unit from hospital information technology (IT), and this project represented one of the first requests for access to EHR Web services from an outside team. As a result, the hand-offs that were necessary to take a request from approval to completion had not been defined, making it difficult to know whether work was in progress or if things had been stalled because a staff member was waiting for additional information. This was resolved by documenting the areas where informatics staff faced difficulty along with suggested solutions, and submitting this to the executive leadership of the hospital IT department. We were then able to collaborate on a more defined process. Once this process was better articulated, frequent communication with the hospital IT staff ensured that continued progress was achieved.

There were several other hurdles faced during the initial implementation that will likely exist at other institutions. First, at CCHMC, like many institutions, there are differences in the underlying EHR environments used for testing and development activities, particularly in whether they were populated with old production data or dummy data. At the time of implementation, the full suite of Web services was not active in all environments. Therefore, we had to use a mix of development and testing services, meaning one service would return real values, while another would return dummy results. This greatly complicated our validation activities. Another challenge was related to the sheer number of Web services available within the EHR. While the EHR contains several hundred native Web services, there are thousands of print groups that can function in the same manner. As a result, there may be hundreds of ways to request a certain type of data. These interfaces have often been created for a specific purpose and apply different filters to the data that are queried, resulting in a unique view of the results. Because of these filters, they can also vary drastically in their performance. Related documentation is sparse, making it difficult to determine which interface to utilize for a given purpose. One potential strategy to address this issue would be for an institution to create a glossary or list of preferred or validated services for a given data type or data domain. This could also be broken down by use case, user base (eg, patient or clinician), or hospital setting (eg, ambulatory versus inpatient) to further streamline the process and shorten development time. Ensuring that the same set of services are also active in every EHR environment (ie, development, testing and production) would also help foster success.

Conclusions

We were able to successfully deploy a mobile app with a custom user interface that can integrate with the EHR to retrieve laboratory results and appointment information using vendor-provided Web services. We used the MyChart services for authentication and authorization, allowing families to utilize their same usernames and passwords to log in. The use of ethnographic design provides an opportunity for researchers to work with stakeholders to identify and develop new interfaces or methods of interacting with the EHR that can serve needs that are not being met with current approaches. It is possible to do this using technology that exists at most institutions. The ethnographic design process itself is best served when informatics development staff are engaged along with the interviewees. Informatics staff can be upfront about any potential challenges in requesting a certain feature, which can be worked into the design and help manage expectations. Developers should expect to face hurdles when integrating with the EHR, but many of them can be addressed with frequent communication and thorough documentation. Continued executive sponsorship is also a key factor, especially the first few times these projects are attempted. In the end, a repeatable process should be achievable, allowing the development of such apps to occur more frequently.

Acknowledgments

This work was supported by funding from the National Institutes of Health – National Institute for Nursing Research (R01NR014248) to co-principal investigators Pai and Mullins.

Conflicts of Interest

None declared.

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Abbreviations

CCHMC: Cincinnati Children's Hospital Medical Center
COG: Children's Oncology Group
EHR: electronic health record
ESO: education and support only
IMPACT: Illness Management and Parental Adjustment to Cancer Treatment
IT: information technology
NCI: National Cancer Institute
NLM: National Library of Medicine
OUHSC: University of Oklahoma Health Sciences Center
RCT: randomized controlled trial
XML: Extensible Markup Language

Edited by G Eysenbach; submitted 16.02.17; peer-reviewed by M Peeples, J Kildea; comments to author 05.04.17; revised version received 25.05.17; accepted 25.05.17; published 26.06.17.

Please cite as:
Marsolo K, Shuman W, Nix J, Morrison CF, Mullins LL, Pai ALH
Reducing Parental Uncertainty Around Childhood Cancer: Implementation Decisions and Design Trade-Offs in Developing an Electronic Health Record-Linked Mobile App
JMIR Res Protoc 2017;6(6):e122
URL: http://www.researchprotocols.org/2017/6/e122/
doi:10.2196/resprot.7523
PMID:28652227

Original Paper

The Feasibility and Acceptability of a Web-Based Alcohol Management Intervention in Community Sports Clubs: A Cross-Sectional Study

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Abstract

Background: The implementation of comprehensive alcohol management strategies can reduce excessive alcohol use and reduce the risk of alcohol-related harm at sporting venues. Supporting sports venues to implement alcohol management strategies via the Web may represent an effective and efficient means of reducing harm caused by alcohol in this setting. However, the feasibility and acceptability of such an approach is unknown.

Objective: This study aimed to identify (1) the current access to and use of the Web and electronic devices by sports clubs; (2) the perceived usefulness, ease of use, and intention to use a Web-based program to support implementation of alcohol management policies in sports clubs; (3) the factors associated with intention to use such a Web-based support program; and (4) the specific features of such a program that sports clubs would find useful.

Methods: A cross-sectional survey was conducted with club administrators of community football clubs in the state of New South Wales, Australia. Perceived usefulness, ease of use and intention to use a hypothetical Web-based alcohol management support program was assessed using the validated Technology Acceptance Model (TAM) instrument. Associations between intention to use a Web-based program and club characteristics as well as perceived ease of use and usefulness was tested using Fisher's exact test and represented using relative risk (RR) for high intention to use the program.

Results: Of the 73 football clubs that were approached to participate in the study, 63 consented to participate and 46 were eligible and completed the survey. All participants reported having access to the Web and 98% reported current use of electronic devices (eg, computers, iPads/tablets, smartphones, laptops, televisions, and smartboards). Mean scores (out of a possible 7) for the TAM constructs were high for intention to use (mean 6.25, SD 0.87), perceived ease of use (mean 6.00, SD 0.99), and perceived usefulness (mean 6.17, SD 0.85). Intention to use the Web-based alcohol management program was significantly associated with perceived ease of use (*P*=.02, RR 1.4, CI 1.0-2.9), perceived usefulness (*P*=.03, RR 1.5, CI 1.0-6.8) and club size (*P*=.02, RR 0.8, CI 0.5-0.9). The most useful features of such a program included the perceived ability to complete program requirements within users' own time, complete program accreditation assessment and monitoring online, develop tailored action plans, and receive email reminders and prompts to complete action.

Conclusions: A Web-based alcohol management approach to support sports clubs in the implementation of recommended alcohol management policies appears both feasible and acceptable. Future research should aim to determine if such intended use leads to actual use and club implementation of alcohol management policies.

(JMIR Res Protoc 2017;6(6):e123) doi:10.2196/resprot.6859

KEYWORDS

alcohol; sports; implementation; technology; TAM; Web; Internet; eHealth

Introduction

Worldwide, approximately 3.3 million deaths and over 200 diseases and injuries are attributable to excessive alcohol consumption [1]. High levels of alcohol consumption and alcohol-related harm have been reported among players and supporters of community level, nonelite sports clubs [2,3]. For instance, in New Zealand nonelite sportspeople have reported higher levels of harmful alcohol consumption (51%) than nonsports people (31%) [4], and nonelite Gaelic football and hurling players in Ireland have reported higher levels of alcohol consumption (32%) compared to a national representative sample of men of a similar age (15%) [3]. Similarly, reported levels of alcohol consumption of nonelite football players in Australia are between 4 and 9 times the recommended level of alcohol per drinking session [2,5].

In many nations, nonelite community sports clubs provide opportunities for organized sports participation for children and adults. A number of characteristics of such community sports clubs make them an attractive setting to address risky alcohol use and alcohol-related harm among players and supporters. First, sports clubs provide access to large numbers of players, spectators, and officials [6]. For instance, in England between 2015 and 2016, 15.83 million people 16 years or over (36.1%) engaged in sport at least once a week [7] and, in Australia, between 2013 and 2014, approximately 5.2 million Australians aged 15 years and over (28%) were involved with organized sport and physical activity [8]. Second, despite community sports clubs being required to adhere to liquor licensing laws regarding responsible service of alcohol [9-11] to reduce the risk of excessive alcohol consumption and alcohol-related harm [12], such adherence is poor [13,14]. For example, a study conducted in 87 community football clubs in New South Wales (NSW), Australia, found 32% did not have all bar staff trained in the Responsible Service of Alcohol (RSA), 38% conducted high-risk drink promotions, and 35% allowed bar staff to consume alcohol while on duty [14]. Third, research has found that community sports clubs are amenable to support to improve alcohol management to reduce alcohol use and harm occurring at these venues [15,16].

Studies have demonstrated that implementing comprehensive alcohol management policies (eg, responsible service of alcohol and inhibiting alcoholic drink promotions) in licensed venues can reduce harmful alcohol use in such premises [17,18]. Similarly, evidence suggests that the implementation of comprehensive alcohol management policies by sporting clubs can reduce excessive alcohol consumption by members in these venues and their risk of alcohol-related harm [19]. For example, in a randomized controlled trial (RCT) of an alcohol management accreditation program in community football clubs in Australia, clubs received face-to-face and telephone-based support to implement a suite of policies to reduce the risk of excessive alcohol use [14]. Postintervention, a significantly greater proportion of intervention clubs (88%) implemented alcohol management policies compared to control clubs (65%), and a significantly lower proportion of club members from intervention group clubs engaged in risky alcohol consumption at the club compared to control clubs [14].

The ability to modify the policies of service delivery organizations is suggested to be enhanced by the use of a variety of evidence-based implementation change strategies such as audit and feedback, consensus processes, training and resource provision [20]. In an RCT of an alcohol management accreditation program in community football clubs in Australia, a number of such strategies were provided on a face-to-face and telephone basis to support the implementation of alcohol management policies. The delivery of implementation support in this manner can represent a logistical and resourcing challenge when a large number of sites (eg, sports clubs, hospitals, schools) are involved and when such sites are geographically dispersed or remote [21]. Computer or Web-based delivery of policy change strategies have become increasingly common and have been shown to be efficacious in improving implementation of evidence-based policies in some settings, such as primarily health care services [22]. For example, in health care settings, Web-based delivery of training, audit, and feedback strategies have been reported to be effective in modifying the provision therapeutic interventions by clinicians [23].

Web-based programs can be delivered at relatively low cost to large numbers of sports clubs and may represent a potential means of overcoming the logistical challenges of scaling up evidence-based alcohol management policies in this setting. Internet coverage is almost universal in high income countries such as Australia [24], extending into rural and remote geographic locations, enabling the provision of Web-based support to clubs located in these areas. Furthermore Web-based programs provide consistent, standardized delivery of content, can tailor content to specific needs of users, and have the functionality to incorporate evidence-based techniques to support implementation (eg, performance monitoring and feedback, action planning and goal setting, and social comparison) [25-29]. While Web-based programs have been used to support implementation or support quality improvement initiatives in other settings, such as hospitals, general health care [22,30], and schools [31-33] we are not aware of evaluations of such initiatives in the sporting club environment.

Despite the potential of Web-based programs, the benefits of such programs are often encumbered by low user engagement and uptake [30,34]. Given this risk of nonutilization, assessment of the feasibility and acceptability of Web-based technologies to end-users has been recommended before significant investments in the development of Web-based programs are initiated [35,36]. The Technology Acceptance Model (TAM) is a validated, widely used, and recommended tool to pre-assess factors associated with end-user intention to use a Web-based program (perceived ease of use and perceived usefulness) [36,37] and to assess the potential use and impact of Web-based technologies. Given the lack of empirical studies examining the use of Web-based programs by sports clubs and club administrators generally and of the potential of such programs to support club implementation of alcohol management policies specifically, a study was undertaken to assess the following:

1. Current access to and use of the Web and electronic devices by community sports club administrators
2. Administrator perceptions regarding the usefulness and ease of use of a hypothetical Web-based support program to support club implementation of alcohol management policies and their intention to use such a program
3. Factors associated with intention to use a Web-based alcohol management support program
4. Specific features of such a program that sports club administrators would find useful

Methods

Design and Setting

A cross-sectional survey of club administrator representatives from community football clubs was conducted in the state of NSW, Australia. Clubs were based in major city, regional, and rural communities.

Participant Eligibility and Recruitment

Football Clubs

Participating clubs were community level, nonelite football clubs across the 4 major Australian football codes: Rugby League, Rugby Union, Soccer/Association football, and Australian Football League. Eligible clubs had players over the legal drinking age (18 years of age and over), were a nonelite community sports club (defined as clubs not involved with a major national or state level league or competition), had over 40 members, and held a current liquor license enabling sale of alcohol at the sports club and were currently participating in an existing alcohol management program delivered on a face-to-face basis (Good Sports) [38]. Additionally, clubs had participated in an RCT conducted between 2009 and 2012, which evaluated the effectiveness of a face-to-face alcohol management program to support clubs to implement alcohol management policies [14]. A full description of the intervention has been published [14]; in short, the intervention included hard copy resources, club committee engagement, and face-to-face monitoring and feedback for each intervention club.

Football Club Administrators

A senior club administrator (eg, president, vice president, or secretary) of eligible clubs was identified from club records and sent a study information letter and invited to participate in the study on behalf of the club.

Data Collection Procedures

An expert advisory group with representation from community sports clubs (senior club administrators), health promotion practitioners, implementation and behavioral scientists, and experts in organizational change informed the development of a computer-assisted telephone interview (CATI) survey, based on previously implemented surveys in sports clubs and other community settings [14,39]. The CATI was piloted on a subsample of community football club administrator representatives to ensure survey language and length was appropriate. Surveys were conducted by trained interviewers in the Australian winter football season (June-August) of 2015. The average length of the survey was 40 minutes.

Measures

Football Club and Club Administrator Characteristics

Club administrators were asked to report the club's home ground postcode, football code (Rugby League, Rugby Union, Soccer/Association football, or Australia Football League), the number of senior (18 years of age and over) and junior (under 18 years of age) teams registered with the club, their current role within the club, the time (in years) they had been in that role, their age, and their gender.

Football Clubs' Current Use of the Web and Electronic Devices

Club administrators were asked to report whether they had access to the Internet and whether they used electronic devices (eg computers, iPads/tablets, smartphones, laptops, televisions, and smartboards) to complete specific club-related tasks (at any location), including membership and player registration, game scheduling, managing club finances/book keeping, communicating with members, committee administration tasks, administration fundraising, and other events.

Perceived Usefulness, Ease of Use, and Intention to Use a Web-Based Alcohol Management Program

The TAM is a validated instrument for prospectively assessing end-user intention to use Web-based programs [36,37]. TAM consists of 3 primary constructs (behavioral intention, perceived ease of use, and perceived usefulness) for which a meta-analysis of 88 studies has reported high internal consistency among each construct (Cronbach alpha score of >0.8) [40]. Derived from the theory of reasoned action, TAM postulates that behavioral intention is linked to actual behavior [36,41]. A systematic review of the TAM literature supports this, with a positive correlation of association between behavioral intention and actual use of technology found for 90% of included studies [35].

A total of 11 items from TAM were adapted for relevance to the sports club setting. A hypothetical Web-based program was described to club administrators via the CATI to determine clubs' perceived usefulness, ease of use, and intention to use

the program to support club implementation of recommended alcohol-management policies. The program was described to club administrators as able to monitor their progress of alcohol policy implementation, provide tailored feedback on their level of implementation, send prompts and reminders for required tasks, and provide unrestricted access to information and resources. Similar adaptation of the TAM has been employed in other community settings [39]. Club administrators were asked to rate on a 7-point scale (1=strongly disagree, 4= neither agree nor disagree, and 7=strongly agree) the perceived usefulness of a Web-based alcohol management program (4 items), the perceived ease of use of such a program (4 items), and their intention to use such a program (3 items) (see Multimedia Appendix 1 for modified TAM questionnaire, including a description of the hypothetical Web-based program).

Specific Features of an Alcohol Management Web-Based Program That Sports Club Administrators Would Find Useful

A total of 10 questions were used to assess the perceived usefulness of specific Web-based program features to support club implementation of an alcohol management program. Responses were recorded on a 7-point scale (1=strongly disagree and 7=strongly agree). Assessed program features were ability to complete program requirements in users' own time, ability to complete program accreditation assessment and monitoring online, development of tailored action plans, email reminders and prompts to complete action items, access to support tools and resources, access to training and educational videos or interactive activities, program support via email or live chat, ability to communicate with club members (email), ability to communicate with other sports clubs in the program, and program-related peer comparison.

Statistical Analysis

Statistical analyses were conducted in SAS version 9.3 statistical software (SAS Institute Inc). Clubs were grouped by football code (Rugby League, Rugby Union, Soccer/Association football, and Australian Rules Football), and classified according to geographical location (major city or inner regional/outer regional) using the Australian Standard Geographical Classification (ASGC) based on the Accessibility/Remoteness Index of Australia score (ARIA) and size (small [≤10 teams] or large [>10 teams]). All statistical tests were 2-tailed with an alpha of 0.05.

For aim 1, simple descriptive statistics were used to describe sports club administrators' access to and use of the Web and electronic devices to undertake club tasks. For aim 2, similar to other TAM studies [39,42], the mean score and standard deviation for each TAM construct was calculated. The internal consistency of each TAM construct was assessed using Cronbach alpha.

For aim 3, again similar to other TAM studies [39,42], the 3 TAM constructs were dichotomized into a score of 1 (strongly disagree) to 5.9 (slightly agree) or 6 (agree) to 7 (strongly agree). By choosing this cut-point, the results allow for a clinically meaningful interpretation, as the median score of the constructs were used. Additionally, this dichotomized score differentiates between those who disagree or only slightly agree to those who have full to strong agreement with the items examined within the TAM constructs. Fisher's exact test was used to test the significance of association between club administrator intention to use the Web-based program (1.0-5.9 [low intention] vs 6.0-7.0 [high intention]), club geographic location, size, administrator age (≤50 years vs >50 years), use of electronic device for club tasks (≥1 device vs no devices), access to the Internet when undertaking club tasks (yes vs no), perceived ease of use of the Web-based support program (construct mean score dichotomized: 1.0-5.9 [low perceived ease of use] vs 6.0-7.0 [high perceived ease of use]), and perceived usefulness of the Web-based support program (construct mean score dichotomized: 1.0-5.9 [low perceived usefulness] vs 6.0-7.0 [high perceived usefulness]). For aim 4, descriptive statistics were used to summarize the features of a Web-based support program that sports clubs administrators agreed or strongly agreed that they would find useful to support implementation of recommended alcohol management policies.

Ethics Approval

Ethics approval was obtained from The University of Newcastle, Human Research Ethics Committee (H-2008-0432).

Results

Football Club and Club Administrator Characteristics

A total of 73 community sporting clubs were approached to participate in the study, of which 63 consented to participate (86%). Of these 63, 17 were ineligible and 46 completed the survey (73% of eligible). Of the participating clubs, the largest proportion were Rugby League clubs (15/46, 33%) and Rugby Union clubs (14/46, 30%), the majority of clubs (38/43, 88%) were located in major cities, and just over half the sample (24/46, 53%) was classified as large clubs. Most club administrator representatives held the role of club president (15/46, 33%) or secretary (14/46, 30%) and were male (39/46, 85%), with a mean age of 48 years and a mean number of 4.3 years in that position (Table 1).

Football Clubs' Current Use of and Access to the Web and Electronic Devices

Most (98%) football club administrators reported current use of electronic devices for club-related tasks and all reported having access to the Web when undertaking these tasks. The proportion of clubs that reported undertaking specific tasks using electronic devices is reported in Table 2.

Table 1. Football club and club administrator representative characteristics (N=46).

Characteristics	Number
Football club characteristic	
Football code	
Australian League Football, n (%)	6 (13)
Rugby League, n (%)	15 (33)
Soccer/Association football, n (%)	11 (24)
Rugby Union, n (%)	14 (30)
Geographical region[a]	
Major city, n (%)	38 (88)
Inner/outer regional, n (%)	5 (12)
Club size	
Small (≤ 10 teams), n (%)	21 (47)
Large (>10 teams), n (%)	24 (53)
Club administrator characteristics	
Club role	
President, n (%)	15 (33)
Vice President, n (%)	4 (9)
Secretary, n (%)	14 (30)
Treasurer, n (%)	4 (9)
Coach, n (%)	1 (2)
Committee member, n (%)	2 (4)
Time in club role, years, mean (SD)	4.3 (3.2)
Age, years, mean (SD)	49 (9.64)
Gender, male, n (%)	39 (85)

[a]N=43.

Table 2. Proportion of clubs reporting the use of the electronic devices to undertake specific club-related tasks (N=46).

Club-related task	n (%)
Membership and player registration	45 (98)
Game scheduling	38 (83)
Managing club finances/bookkeeping	44 (96)
Communicating with members	45 (98)
Committee administration tasks	45 (98)
Administration fundraising and other events	44 (96)

Table 3. Football clubs perceived usefulness, ease of and intention to use a Web-based program to support implementation of recommended alcohol management policies.

TAM[a] items and constructs	Mean (SD)
Perceived usefulness	
I would find Good Sports online useful in helping my club implement Good Sports policies.	6.30 (0.70)
Using Good Sports online would improve my clubs PERFORMANCE in implementing Good Sports policies.	6.20 (0.96)
Using Good Sports online would increase my clubs PRODUCTIVITY in implementing Good Sports policies.	6.07 (1.04)
Using Good Sports online would help enhance the EFFECTIVENESS of my club in implementing of Good Sports policies.	6.11 (0.97)
Overall usefulness of Good Sports online [b]	6.17 (0.85)
Perceived ease of use	
My interaction with Good Sports online would need to be clear and understandable.	6.33 (0.97)
Interacting with Good Sports online is not likely to require a lot of my mental effort.	5.83 (1.32)
I would find Good Sports online easy to get it to do what I want it to do.	5.89 (1.16)
I would find Good Sports online easy to use.	5.96 (1.09)
Overall perceived ease of use of Good Sports online [b]	6.00 (0.99)
Perceived intention of use	
Assuming I had access to Good Sports online, I INTEND to use it.	6.24 (0.92)
Given that I had access to Good Sports online, I PREDICT that I would use it.	6.24 (0.90)
If Good Sports online was currently available, I would PLAN to use it in the next 12 months.	6.28 (0.91)
Overall intention to use Good Sports online [b]	6.25 (0.87)

[a]TAM: Technology Acceptance Model.

[b]Cronbach alpha score of >0.9 for each TAM construct: usefulness, perceived ease of use, and intention to use a Web-based program.

Perceived Usefulness, Ease of Use, and Intention to Use a Web-Based Alcohol Management Implementation Program

Table 3 presents the mean score and standard deviation for each individual TAM question and overall for each of the 3 TAM constructs. Internal consistency for each construct was high, with a Cronbach alpha score of >0.9 for each of the 3 TAM constructs. For all 11 items within the TAM domains club administrators had high scores, with a mean score of 5.83 or greater (max 7) for all items. The perceived usefulness of a Web-based program to help sports clubs implement recommended alcohol management policies was high; with an overall mean construct score of 6.17 (SD 0.85). Similarly, the perceived ease of use (construct mean 6.00, SD 0.99) and intention to use such a Web-based support program were high (construct mean 6.25, SD 0.87). A total of 89% of clubs reported a high behavioral intention to use a Web-based alcohol management program.

Club and Administrator Characteristics and Perceptions Associated With Perceived Intention to Use a Web-Based Alcohol Management Program

Table 4 presents the results of tests of association between club and administrator characteristics and perceived ease of use, perceived usefulness, and perceived intention to use a Web-based program to support implementation of alcohol management policies. The characteristics that were found to be positively associated with high intention to use a Web-based alcohol management program were perceived ease of use (P=.02) and perceived usefulness of the program (P=.03). Club size was found to be positively significantly associated with high intention to use such a program (P=.02).

Table 4. Associations between club and administrator characteristics and perceptions and intention to use a Web-based alcohol management program.

Characteristics and perceptions	Intention to use[a]		Relative risk for high intention of use	Fisher's exact *P* value
	Score of 1.0-5.9 N=5 n (%)	Score of 6.0-7.0 N=41 n (%)	RR (95% CI)	
Geographical region[b]				.48
Major city	4 (11)	34 (89)	1.1 (0.8-4.4)	
Inner/outer regional	1 (20)	4 (80)	—	
Club size				.02
Small	5 (24)	16 (76)	0.8 (0.5-0.9)	
Large	0 (0)	24 (100)	—	
Club administrator age				.65
50 years or less	2 (8)	23 (92)	1.1 (0.8-1.5)	
Over 50 years	3 (14)	18 (86)	—	
Current use of electronic devices for club tasks				1.00
1 or more devices	5 (11%)	40 (99%)	0.9 (0.7-30.8)	
No devices	0 (0%)	1 (100%)	—	
Access to internet when undertaking club tasks				1.00
Yes	5 (11%)	40 (89%)	—	
No	0 (0%)	0 (0%)	—	
Perceived ease of use[a]				.02
1.0-5.9	4 (31%)	9 (69%)	—	
6.0-7.0	1 (3%)	32 (97%)	1.4 (1.0-2.9)	
Perceived usefulness[a]				.03
1.0-5.9	3 (37%)	5 (63%)	—	
6.0-7.0	2 (5%)	36 (95%)	1.5 (1.0-6.8)	

[a]Score of 1.0-5.9 indicates response to statements of strongly disagree to slightly agree, and score of 6.0-7.0 indicates response to statements of agree and strongly agree.

[b]Clubs categorized using the Australian Standard Geographical Classification (ASGC), which classifies remoteness based on sports clubs postcodes matching the Accessibility/Remoteness Index of Australia (ARIA) score.

Specific Features of an Alcohol Management Web-Based Program That Sports Club Administrators Reported Would Be Useful

Overall, there was a high level of agreement regarding the usefulness of each of the proposed program features. All club administrators agreed or strongly agreed that the ability to complete program requirements within their own time would be a useful feature. Greater than 90% of club administrators agreed or strongly agreed that it would be useful for the program to enable completion of program accreditation assessment and monitoring online (96%), develop tailored action plans (96%), send email reminders and prompts to complete actions (96%), provide access to support tools and resources (96%), include program support (email or live chat) (94%), and provide program-related peer comparison (91%). A high level of support was evident for access to videos or interactive activities for training and education (83%), an ability to communicate with club members by email (78%), and an ability to communicate with other sports clubs in the program (70%).

Discussion

Principal Findings

This is the first study to assess the feasibility and acceptability of a Web-based program to support the implementation of alcohol management policies by community sports clubs. There was universal access to the Web and use of electronic devices when undertaking club-related tasks among clubs. The vast majority (89%) of club administrators reported high behavioral intention to use a Web-based program to support their club's implementation of recommended alcohol management policies. Furthermore, both perceived usefulness of a Web-based alcohol management program and its perceived ease of use were positively associated with intended use. The findings suggest that there is considerable potential for a Web-based program to support sports clubs in the implementation of recommended

alcohol management policies and in doing so to make a contribution to reducing alcohol-related harm in this setting and the community at large.

The study findings are comparable to similar studies conducted in other settings. For example, high intention to use Web-based programs to support implementation of health-related programs have been reported in childcare services [39], health care centers [43], and other community settings [42]. Furthermore, significant associations between perceived ease of use or perceived usefulness of Web-based programs with their intended use has been consistently reported across settings [37,39,43]. To ensure a high level of perceived ease of use and usefulness, such findings underscore the importance of program features designed to address barriers to engagement (eg, assimilation and personalization reduction) [27,44] and the importance of formative research with end-users to ensure the development of useful programs that meet their needs.

In this study, larger clubs had a significantly higher level of intended program use (100%) compared to smaller clubs (76%). This may be due to greater complexity of managing alcohol use in larger clubs, requiring greater workforce, resources, and infrastructure to manage. Potentially, the use of Web-based programs to coordinate the implementation of alcohol management policies in these settings may be perceived as of greater benefit. Similarly, as in licensed venues, sports clubs experience a high number of alcohol-related incidents [45,46], Web-based support to reduce such alcohol-related harm may be more salient among administrators of larger clubs. Nonetheless, the findings suggest that Web-based support may be less effective in supporting improvements in alcohol management in smaller clubs. Future research to identify alternate and adjunctive models of support for such clubs appears warranted.

Strengths and Limitations

The results of this study should be considered with respect to its strengths and limitations. The strengths of this study include the application of a validated tool [40] to assess intended use of a hypothetical Web-based program, strong internal consistency across TAM constructs, and complete data for all participants. On the other hand, while club administrators are those most likely to be coordinating and overseeing the introduction of a Web-based program to support the implementation of recommended alcohol management policy, it is possible that they may not be representative of all individuals involved with clubs that may at times use such a program, such as volunteers and other staff. Clubs in this study were randomized into either the intervention or control arm of a face-to-face alcohol management trial between 2009 and 2012 [14], thus some of the clubs would have received intensive intervention support throughout this time. Therefore, it should be noted that previous intervention clubs within this group may be more likely to find it feasible and acceptable to use a Web-based program to support alcohol policy implementation. In addition, findings from this study may not be able to be generalized to groups outside of the study sample, such as other sporting codes or other community organizations. Finally, although there is empirical evidence [35] to show that intended use of a program is linked to actual use, actual rates of use of a Web-based program to support the implementation of recommended alcohol management policies among participants in this setting has not been reported.

Conclusion

Further studies are required to determine if sports clubs will actually use such a program if it existed and to show whether such a program has the intended effect of supporting clubs to implement recommended alcohol management policies.

Acknowledgments

The research team acknowledges the funding support of Australian Research Council, Hunter New England Population Health, the Alcohol and Drug Foundation, The University of Newcastle, and the Hunter Medical Research Institute. The research team would also like to acknowledge the support of the project staff involved in this study and the interviewers involved in collecting outcome data from club administrator representatives.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Modified Technology Acceptance Model questionnaire (administered via computer-assisted telephone interview).

[PDF File (Adobe PDF File), 54KB - resprot_v6i6e123_app1.pdf]

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Abbreviations

ARIA: Accessibility/Remoteness Index of Australia
ASGC: Australian Standard Geographical Classification
CATI: computer-assisted telephone interview
NSW: New South Wales
RCT: randomized controlled trial
RR: Relative Risk
RSA: Responsible Service of Alcohol
TAM: Technology Acceptance Model

Edited by G Eysenbach; submitted 20.10.16; peer-reviewed by J Wright, K Ohara; comments to author 28.01.17; revised version received 16.02.17; accepted 04.03.17; published 30.06.17.

Please cite as:
McFadyen T, Wolfenden L, Wiggers J, Tindall J, Yoong SL, Lecathelinais C, Gillham K, Sherker S, Rowland B, McLaren N, Kingsland M
The Feasibility and Acceptability of a Web-Based Alcohol Management Intervention in Community Sports Clubs: A Cross-Sectional Study
JMIR Res Protoc 2017;6(6):e123
URL: http://www.researchprotocols.org/2017/6/e123/
doi:10.2196/resprot.6859
PMID:28666977

Protocol

Stroke Avoidance for Children in REpública Dominicana (SACRED): Protocol for a Prospective Study of Stroke Risk and Hydroxyurea Treatment in Sickle Cell Anemia

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Abstract

Background: In the Dominican Republic, where the burden of sickle cell anemia (SCA) is high, many children lack access to routine screening and preventative care. Children with SCA are at risk for stroke, an event that leads to significant morbidity and mortality. In the United States, screening via transcranial Doppler (TCD) identifies children with SCA at highest stroke risk, allowing early intervention with blood transfusions. The need for indefinite transfusions for primary stroke prevention limits their practicality in limited-resource countries. Hydroxyurea has been shown to lower TCD velocities and to prevent conversion from conditional (170 to 199 cm/sec) to abnormal (greater than or equal to 200 cm/sec) velocities. In resource-limited settings, implementation of a TCD screening program, coupled with hydroxyurea therapy, could reduce the burden of SCA and stroke.

Objective: The aims of the Stroke Avoidance for Children in REpública Dominicana (SACRED) trial are (1) to screen children with SCA for stroke risk using TCD and to determine the prevalence of elevated velocities in a cross-sectional sample; (2) to identify clinical and laboratory correlates of elevated velocities; and (3) to obtain longitudinal data on the natural history of TCD velocities and to measure therapeutic effects of hydroxyurea.

Methods: This prospective trial, designed and conducted by Cincinnati Children's Hospital Medical Center (CCHMC) and Hospital Infantil Robert Reid Cabral (HIRRC) with Centro de Obstetricia y Ginecología, includes a baseline cross-sectional epidemiological survey of the distribution of TCD velocities across a large cohort of children with SCA in the Dominican Republic. Children with conditional velocities are eligible to begin protocol-directed hydroxyurea if laboratory criteria are met. The treatment schedule begins with a fixed-dose of approximately 20 mg/kg/day for 6 months, after which it escalates to maximum tolerated dose (MTD). All participants undergo longitudinal annual TCD evaluation, while those on hydroxyurea have semi-annual evaluations during the 3-year study period. Data are collected using an Internet-based Research Electronic Data Capture (REDCap) system with forms translated into Spanish; both remote and on-site monitoring are used.

Results: To date, 122 children with SCA have enrolled in SACRED including 85 (69.7%, 85/122) with normal, 29 (23.8%, 29/122) with conditional, 5 (4.1%, 5/122) with abnormal, and 3 (2.5%, 3/122) with inadequate TCD velocities. Of the 29 children with conditional TCD velocities, 17 (59%, 17/29) have initiated hydroxyurea per protocol, with plans for escalation to MTD.

Conclusions: The SACRED trial will provide novel epidemiologic data about the prevalence of children with SCA and increased stroke risk in the Dominican Republic. The study also includes an investigation of the impact of hydroxyurea at MTD on elevated

TCD velocities, as well as clinical and laboratory parameters. The design and implementation of SACRED reflect a successful international institutional partnership, one that features local capacity building and training in research methods and clinical care. The trial's results have important implications for screening and prevention of primary stroke in children with SCA living in resource-limited settings.

Trial Registration: ClinicalTrials.gov NCT02769845; https://www.clinicaltrials.gov/ct2/show/NCT02769845 (Archived by WebCite at http://www.webcitation.org/6qf6n0Egh)

(JMIR Res Protoc 2017;6(6):e107) doi:10.2196/resprot.7491

KEYWORDS

Dominican Republic; hydroxyurea; sickle cell anemia; stroke; transcranial Doppler

Introduction

Sickle cell anemia (SCA) is one of the most common inherited red blood cell disorders. Its prevalence is highest in sub-Saharan Africa, but there are also significant disease burdens in the Americas, India, Mediterranean region, and the Caribbean including Jamaica and the Dominican Republic [1]. SCA is associated with high morbidity and mortality, especially in limited-resource settings. Stroke is one of the most devastating clinical events to occur in children with SCA and can lead to considerable morbidity and early mortality. The frequency of primary stroke in children with homozygous hemoglobin S (HbSS), the most common and severe form of SCA, is approximately 5% to 10% [2,3].

Many pediatric sickle cell programs in the United States and Europe use transcranial Doppler (TCD) ultrasound screening to identify children at risk for developing primary stroke. TCD is a means of measuring blood velocity in the circle of Willis. The standard evaluation for stroke risk includes interrogation of the major intracranial vessels in both hemispheres including the middle cerebral artery, anterior cerebral artery, bifurcation of the middle cerebral and anterior cerebral arteries, distal internal carotid artery, posterior cerebral artery, and top of the basilar. In children with SCA, the time-averaged maximum velocity (TAMV) is recorded and normal velocities less than 170 cm/sec are associated with lowest stroke risk, while conditional velocities (170 to 199 cm/sec) and abnormal TCD velocities (200 cm/sec or greater) are associated with increased risk and highest risk, respectively [4]. Adams et al demonstrated that TCD could effectively be used to screen pediatric patients with SCA and found the relative risk of stroke was 44 times greater among patients with TCD velocities above 200 cm/sec [3,4]. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) and subsequent STOP II trials demonstrated that children with abnormal velocities must receive chronic blood transfusions indefinitely to reduce the risk of primary stroke [5,6].

Several centers throughout the world have successfully utilized TCD screening, proving its feasibility in various patient populations [7-12]. TCD screening examinations are typically performed as early as 2 to 3 years of age in children with SCA and then annually thereafter. The natural history is variable, but some patients present with abnormal velocities while most young patients start in the normal or conditional range, and then over time may convert to the abnormal range. In a retrospective study, these increases were more likely in children less than 10 years of age, with 23% of conditional velocities converting to abnormal over an 18-month time period [13]. Young age, low oxygen saturation, severity of anemia, and low levels of fetal hemoglobin are among the demographic and clinical variables reported as correlates of elevated TCD velocities [9,14,15]. In contrast, inheritance of alpha-thalassemia trait has been described in several studies as a protective factor [16-18], whereas the impact of concomitant *glucose-6-phosphate dehydrogenase* (G6PD) deficiency on TCD velocities yields mixed findings [19,20]. In resource-limited settings where access to TCD is limited, identification of additional risk factors could be important for prioritizing patients who warrant early screening.

Hydroxyurea is a disease-modifying medication that induces fetal hemoglobin production [21], reduces the frequency of painful vaso-occlusive episodes [22], and lowers TCD velocities [23,24]. Two prospective multicenter phase 3 clinical trials funded by the National Institutes of Health (NIH) investigated the efficacy of hydroxyurea versus transfusions for stroke prevention in SCA; 90% secondary stroke prevention was observed (NCT00122980) [25] while 100% primary stroke prevention was achieved in children with abnormal TCD velocities (NCT01425307) [26]. A third international multicenter NIH-funded trial investigated the efficacy of hydroxyurea for children with conditional TCD velocities, and demonstrated a significant reduction in mean velocity of 15 cm/sec with no conversions to abnormal velocities and no primary stroke events [27].

The use of hydroxyurea for children with SCA is attractive in limited-resources settings because of its safety, ease of oral administration, and low cost, while its long-term risks appear to be relatively small [28]. Chronic blood transfusions are effective for stroke prevention in SCA but not without challenges including cost, alloimmunization, infection, iron overload, and limited supply in many parts of the world. Accordingly, implementation of TCD screening that is coupled to hydroxyurea treatment represents an important option for resource-limited areas. We previously designed a research protocol (EXTEND, NCT02556099) that utilizes hydroxyurea treatment for both primary and secondary stroke prevention in Jamaica, where chronic blood transfusions are not feasible [29]. The current Stroke Avoidance for Children in REpública Dominicana (SACRED) protocol (NCT02769845) focuses on broad TCD screening and hydroxyurea treatment for prevention of primary stroke, while highlighting another international collaboration within the Caribbean as a prototype for successful research partnerships throughout the world. The trial will

provide novel epidemiologic and treatment data for children with SCA in the Dominican Republic, with significant implications for screening and stroke prevention in resource-limited settings. The purpose of this paper is to describe the trial's implementation, design, and preliminary results.

Methods

Identifying the Knowledge Gap

In the Dominican Republic, an estimated 6% to 8% of the population has the sickle trait, while 0.12% of the population has homozygous SCA (HbSS). Since there is no formal newborn hemoglobinopathy screening program in the country, these numbers are estimates and based on anecdotal data. TCD screening is costly and primarily available to patients in the private sector. The prevalence of elevated TCD velocities in this population is unknown, as is the prevalence of clinical or genetic factors that might influence cerebral blood flow and stroke risk.

Hospital Infantil Robert Reid Cabral (HIRRC) is a large children's hospital and referral center in Santo Domingo, the capital city of the Dominican Republic. Approximately 5.82% (64/1100) registered SCA patients have had overt stroke and receive chronic blood transfusions that are costly and difficult to maintain (unpublished data). The early identification of children with elevated TCD velocities, identification of variables that may predict stroke risk, and early intervention with hydroxyurea would therefore have significant public health implications. Hydroxyurea is available, but not utilized by most patients with SCA. The current clinical practice in the Dominican Republic is to offer hydroxyurea at around 15 mg/kg/day to families who can afford the daily medication, which costs US $1 per capsule. Preliminary data suggest safety and efficacy at a fixed dose in reducing vaso-occlusive crises in this population [30]. However, evaluation of escalation to maximum tolerated dose (MTD) is warranted when the goal is stroke prevention, since improved laboratory results are observed at higher treatment doses [31].

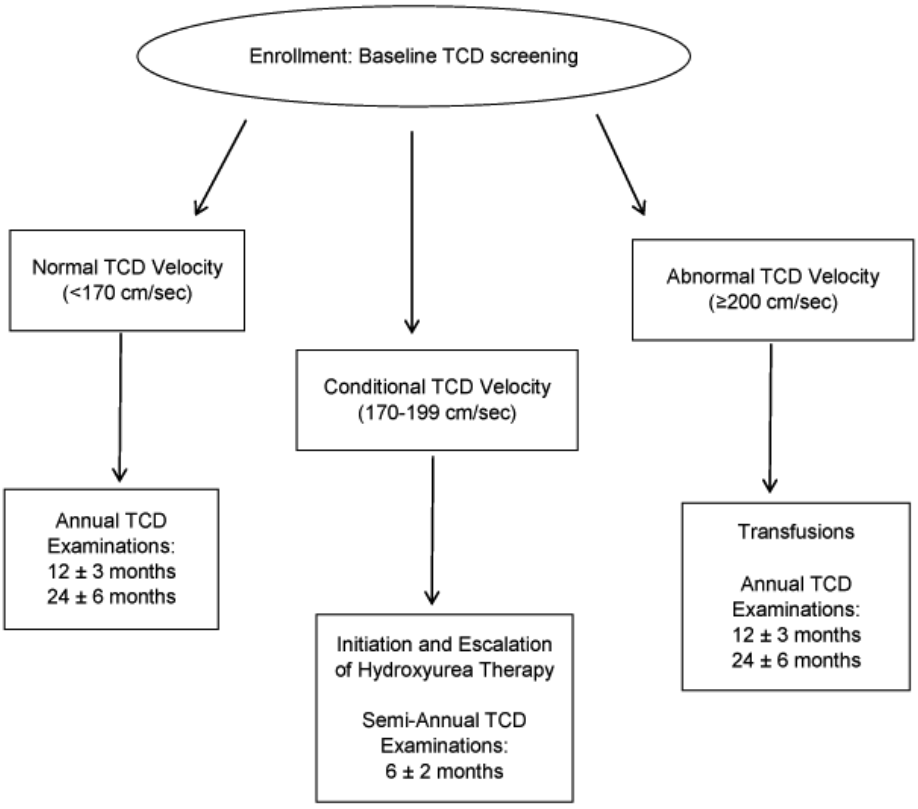
Study Design and Objectives

SACRED involves a 3-part prospective study design which includes (1) baseline TCD evaluation; (2) longitudinal TCD evaluation; and (3) treatment if warranted (Figure 1).

Baseline Transcranial Doppler Evaluation

The baseline evaluation portion of SACRED involves obtaining TCD examinations on children with SCA between ages 3 to 15 years and followed at HIRRC. Up to 500 participants may be enrolled, but projected enrollment is 250 to 300 children over a 12-month period. All patients, including those who are already on hydroxyurea or monthly transfusion therapy (whether for stroke or other clinical indications) are included in study recruitment and TCD screening, to obtain an accurate 1-year cross-sectional description of velocities in the current SCA patient population. Additional baseline assessments will identify potential modifiers that influence cerebral blood flow including age, sex, medical history, hemoglobin concentration, and fetal hemoglobin, as well as genetic variants like G6PD deficiency, beta-globin haplotype, and alpha-thalassemia trait.

Figure 1. Study design.



Longitudinal Transcranial Doppler Evaluation

For the longitudinal aspect of SACRED, participants undergo serial TCD examinations to help define the natural history of cerebrovascular disease in this population. Children on protocol-directed hydroxyurea therapy will undergo TCD every 6 months, while all other participants will have an annual examination.

Protocol-Directed Hydroxyurea Therapy

Children with conditional velocities between 170 to 199 cm/sec are eligible for protocol-directed hydroxyurea therapy, while those with abnormal velocities (200 cm/sec or greater) commence transfusion therapy per current practice guidelines at the clinical site. All participants who are already on chronic transfusion therapy at the time of enrollment, regardless of TCD result, may elect to remain on transfusion therapy per local clinical practice. SACRED participants will be followed until a common study termination date, defined as 3 years from the first participant's initiation of hydroxyurea (Figure 1).

Study Objectives and Hypotheses

The first objective of the SACRED trial is to screen a cohort of children with SCA in the Dominican Republic for stroke risk using TCD and to determine the prevalence of normal, conditional, and abnormal velocities in a cross-sectional sampling of children. Our hypothesis is the distribution of TCD velocities in a cross-sectional sampling of Dominican children will approximate that of prior studies in North America with a distribution of approximately 70% normal, 15% conditional, 10% abnormal, and 5% inadequate [32,33].

The second objective is to identify clinical and laboratory correlates of TCD velocities in a cohort of Dominican children such as age, prior hydroxyurea exposure, level of anemia, fetal hemoglobin, and genetic modifiers such as alpha-thalassemia trait and beta-globin haplotypes. We hypothesize that children with elevated TCD velocities will be younger, lack prior hydroxyurea exposure, have lower total hemoglobin and fetal hemoglobin levels, and higher levels of hemoglobin S (HbS) compared to participants with normal velocities. Beta-globin haplotypes will reveal a mixed genetic inheritance and alpha-thalassemia trait will be protective against elevated velocities.

Our third objective is to obtain longitudinal data on the natural history of TCD velocities in this patient cohort and to measure the effects of therapeutic intervention on TCD velocities, specifically hydroxyurea for conditional TCD velocities and transfusions for abnormal velocities. Given the potential neuroprotective effects of hydroxyurea, we anticipate a lower rate of conversion from conditional to abnormal than the 23% described in a previous observational study [13].

Protocol Training

Training sessions for the local study team occurred remotely and on-site. Study personnel completed online Human Subjects Protection training via NIH training modules available in Spanish. An on-site investigators' meeting occurred 6 months prior to study activation in which Cincinnati Children's Hospital Medical Center (CCHMC) team members conducted protocol training, as well as training on informed consent, TCD, laboratory collection, hydroxyurea dosing calculator, pharmacy storage, adverse event reporting, and the Research Electronic Data Capture (REDCap) database. The Data Management Center (DMC) provided additional REDCap training in-person and remotely via Skype. Study coordinators utilized a training environment in the REDCap system in which they entered data for all case report forms on mock patients, which were verified and queried by the study monitor. Upon completion of REDCap training, coordinators were provided with an official certificate and access to the database. TCD training occurred over several months, with initial hands-on training by the CCHMC TCD coordinator. The local examiners then completed practice exams with upload and remote verification by the TCD coordinator. An official certificate was provided when the TCD coordinator verified that each local examiner had met certification criteria. SACRED Medical Coordinating Center (MCC) representatives from CCHMC were present for study activation and initial enrollment in July 2016.

Study Setting

Participant recruitment, enrollment, TCD screening, and medical examinations occur at the primary clinical site at HIRRC. All evaluations are conducted by local team members who have completed the training as detailed above. Two study assessments—brain magnetic resonance imaging/magnetic resonance angiogram (MRI/MRA) and urine pregnancy tests for post-menarchal females on hydroxyurea therapy—occur at a partnering site, Centro de Obstetricia y Ginecología, also located in Santo Domingo. CCHMC serves as both the MCC and the DMC for the trial. SACRED was approved by the CCHMC institutional review board (IRB) on March 16, 2016, as well as 2 ethics boards in the Dominican Republic: Comité del Centro Nacional de Investigación en Salud Materno Infantil (CENISMI, through HIRRC) on April 29, 2016 and Consejo Nacional de Bioética en Salud (CONABIOS, National board) on June 28, 2016.

Participant Recruitment and Enrollment

Children seen in the hematology clinic at HIRRC are invited to participate in SACRED. The informed consent document is signed by a parent or legal guardian, with assent as required by the local ethics board for all children 10 years and older. Consent includes acknowledgment of storage of genetic material. Inclusion criteria include (1) pediatric patients with severe forms of SCA (HbSS or HbS beta^0-thalassemia); and (2) between 3 and 15 years of age at the time of enrollment. There are no exclusion criteria applicable to the baseline or longitudinal TCD screening portion of SACRED, but for participants with conditional TCD velocities, the following criteria disqualify them from treatment with hydroxyurea: (1) known medical condition making participation ill-advised (eg, acute or chronic infectious disease, known allergy to hydroxyurea, or malignancy); or (2) pregnancy. Participants with abnormal baseline laboratory values, defined as hemoglobin less than 6.0 gm/dL, absolute reticulocyte count (ARC) less than 100 x 10^9/L with a hemoglobin less than 8.0 gm/dL, absolute neutrophil count (ANC) less than 1.0 x 10^9/L, platelet count less than 80 x 10^9/L, or elevated serum creatinine are temporarily excluded

from starting hydroxyurea until improvement of the affected laboratory parameter into the acceptable range.

Study Procedures and Treatment

For the schedule of evaluations, see Table 1. All enrolled participants undergo baseline TCD evaluation, medical history, physical examination, and laboratory analysis. The laboratory analysis includes complete blood count (CBC) with differential, reticulocyte count, serum chemistry, hemoglobin electrophoresis, and special studies to include saved serum and collection of blood onto Whatman Flinders Technology Associates cards (FTA) to be sent in batches to CCHMC for genetic analysis including testing for alpha-thalassemia trait, G6PD deficiency, and beta-globin haplotype. A child identified to have an abnormal velocity (200 cm/sec or greater) is scheduled for a repeat TCD within 3 weeks, and if confirmed to be abnormal, initiates erythrocyte transfusions per local standard of care. Children who are not treated with hydroxyurea per SACRED undergo annual evaluation (Figure 1).

Table 1. Schedule of study evaluations.

Evaluation	Enrollment	Year 1[a]	Year 2[b]
Medical history[c]	Yes	Yes	Yes
Prior/concomitant medications[c]	Yes	Yes	Yes
Physical examination[c]	Yes	Yes	Yes
Labs (complete blood count with differential, reticulocyte count)[c]	Yes	Yes	Yes
Hemoglobin electrophoresis	Yes	No	No
Hemoglobin F level[d]	Yes	Yes	Yes
TCD[e] examination[f]	Yes	Yes	Yes
Special studies[g]	Yes	No	No
Brain MRI/MRA[h] for participants on hydroxyurea only	Yes	No	Yes

[a]Year 1 is 12 months plus or minus 3 months.

[b]Year 2 is 24 months plus or minus 6 months.

[c]Participants on hydroxyurea will undergo these evaluations monthly until reaching maximum tolerated dose (MTD) and then quarterly after MTD is reached.

[d]Quarterly for participants on hydroxyurea.

[e]TCD: transcranial Doppler.

[f]Every 6 months for participants on hydroxyurea.

[g]Special studies includes specimens for genomic DNA analysis and serum biomarkers. Will be additionally collected at study exit for children on hydroxyurea.

[h]MRI/MRA: magnetic resonance imaging/magnetic resonance angiogram.

Children identified to have a conditional TCD (170 to 199 cm/sec) are eligible for protocol-directed hydroxyurea treatment. Additional evaluations for hydroxyurea-treated participants include collection of saliva (DNA Genotek Inc., Ottawa, Canada) to obtain DNA, urine pregnancy test (if applicable), and a brain MRI/MRA around the time of treatment initiation. Brain MRI/MRA images are additionally obtained at study exit for children on hydroxyurea to grade vasculopathy, using previously reported techniques [34] and to evaluate treatment effect. The non-contrast technique includes whole-brain imaging of sagittal T1, axial T1, coronal and axial fluid-attenuated inversion recover (FLAIR), T2-weighted, and diffusion-weighted images. Participants are evaluated clinically and sedation is provided if deemed necessary and parental consent obtained. The sequences are uploaded onto a secure research cloud that deidentifies images and are stored on a CCHMC research server for central review. Participants are aware that the MRI is for research purposes and real-time results are not provided.

Hydroxyurea is purchased locally and provided as generic 500 mg capsules. A hydroxyurea dosing calculator, previously described [35], is available on the SACRED website and provides recommended target dose based on a participant's weight, current laboratory values, and previous dose. During the first 6 months of treatment, participants are administered hydroxyurea at a fixed dose of 20.0 plus or minus 5.0 mg/kg/day. The fixed dose of 20.0 mg/kg/day was selected to ensure hydroxyurea will be tolerated without excessive hematological toxicities; a decision made in conjunction with the local investigators. The large variation in starting dose is due to limitations with having only one available 500 mg capsule size locally. Average daily dosing, in which smaller children take medication on alternate days or skipping days of the week to reach targeted total weekly dose, does not permit precise dosing but has been used previously with success [31,36]. Capsules may be crushed and mixed into liquid for children with difficulty swallowing. During the fixed-dose phase, children undergo monthly study visits that include interval medical history, adverse event reporting, physical examination, and laboratory evaluation with CBC/differential and reticulocyte

count. Every 3 months, fetal hemoglobin levels, serum chemistries, and urine pregnancy tests (if applicable) are obtained. After 6 months, hydroxyurea will be increased to MTD as defined by hematological toxicity, to achieve a target ANC of 2.0-4.0 x 10^9/L. Hydroxyurea dose escalation will occur at 8-week intervals, in increments of 2.5 to 5.0 mg/kg/day. After reaching MTD, study visits occur every 3 months. During all phases of study treatment, medication is temporarily suspended should hematological toxicity, defined as ANC less than 1.0 x 10^9/L, hemoglobin less than 7.5 gm/dL with an ARC less than 100 x 10^9/L, ARC less than 80 x 10^9/L with hemoglobin less than 8.5 gm/dL, or platelet count less than 80 x 10^9/L occur. The dose escalation and toxicity criteria are listed in Table 2. Complications of hydroxyurea therapy and neurological events are collected at interval visits as part of adverse event reporting. Medication adherence is assessed at each visit by parental report and asking participants to bring the medication bottles so the local study team can count the number of returned capsules.

Table 2. Hydroxyurea dose escalation and toxicity criteria.

Toxicity	Parameter	Escalation criteria	Dose-limiting toxicity
Neutropenia	ANC[a] (x10^9/L)	> 4.0	<1.0 x 10^9/L
Anemia	Hemoglobin (gm/dL)	> 6.5	Hb[b] <7.5 gm/dL unless ARC[c] >100 x 10^9/L
Reticulocytopenia	ARC (x10^9/L)	> 150	ARC <80 x 10^9/L unless Hb >8.5 gm/dL
Thrombocytopenia	Platelets (x10^9/L)	> 150	<80 x 10^9/L

[a]ANC: absolute neutrophil count.

[b]Hb: hemoglobin.

[c]ARC: absolute reticulocyte count.

Study data are collected and managed using the REDCap electronic data system [33]. REDCap is a secure, Web-based application designed to support data capture for research studies, providing a platform for data entry and validation, audit trails for tracking data manipulation, and automated export procedures for data analysis. The system uses low bandwidth, rendering it suitable for research in low-income countries, as well as multilingual capabilities including Spanish. Data are entered into the electronic data record directly from the clinical site. Each enrolled participant is assigned a study identification (ID) number, which allows deidentified information to be collected. The DMC reviews data for accuracy and completeness via remote and on-site monitoring. Quality assurance monitoring is performed on the data at standard time intervals per the study's Data Safety Monitoring Plan. Standard database reports, generated monthly, include enrollment, withdrawal, cumulative toxicities, and serious adverse events.

Statistical Analyses

No sample size calculation was performed because the study utilizes a convenience sample. Descriptive analysis of the data from TCD screening will be performed. TCD velocities will be measured longitudinally and summary statistics such as mean, standard deviation, and median for the change of TCD measurements from baseline to study exit will be reported. The primary endpoints of SACRED are changes in TCD velocities over time as a measure of treatment response for participants on hydroxyurea and to evaluate natural history of TCD velocities for those not on treatment. Secondary endpoints will include hydroxyurea-related toxicities and clinical and laboratory correlates of TCD velocities. For patients on treatment, the highest TAMV for each time period along with the baseline values will be analyzed using repeated measures analysis of variance (MANOVA). Participants who are non-adherent to dosing or who are unable to continue hydroxyurea treatment secondary to treatment-associated toxicities will be analyzed according to intention-to-treat. However, hydroxyurea discontinuation dates and adherence information will be recorded for secondary analysis.

Baseline labs will be compared to exit studies for parameters such as hemoglobin, fetal hemoglobin, ANC, ARC, and platelets using descriptive statistics and comparative *t* tests. For analyses of genetic modifiers, single nucleotide polymorphisms (SNPs) from either candidate genes or whole exome sequencing methods will be tested for their association with the phenotypes of interest.

Results

Enrollment began on July 18, 2016. At present, a total of 122 participants have been enrolled (Figure 2). All participants who were approached and met the inclusion criteria have consented for SACRED. The categorical results, shown in Table 3, include 85 (69.7%, 85/122) participants with a normal TCD, while 29 (23.8%, 29/122) have a conditional, 5 (4.1%, 5/122) have an abnormal, and 3 (2.5%, 3/122) have an inadequate TCD. Of the 29 children with conditional velocities, 17 (59%, 17/29) have already initiated protocol-directed hydroxyurea therapy. Of the participants, 22 (18.0%, 22/122) children were already on hydroxyurea at time of enrollment, 2 (9%, 2/22) of whom had conditional velocities and were eligible for treatment on study-directed dosing. The initial baseline screening phase will continue for approximately 12 months from study activation. The common study termination date is 3 years after the first participant began hydroxyurea, which is scheduled for August 2019.

Table 3. Participant status (N=122).

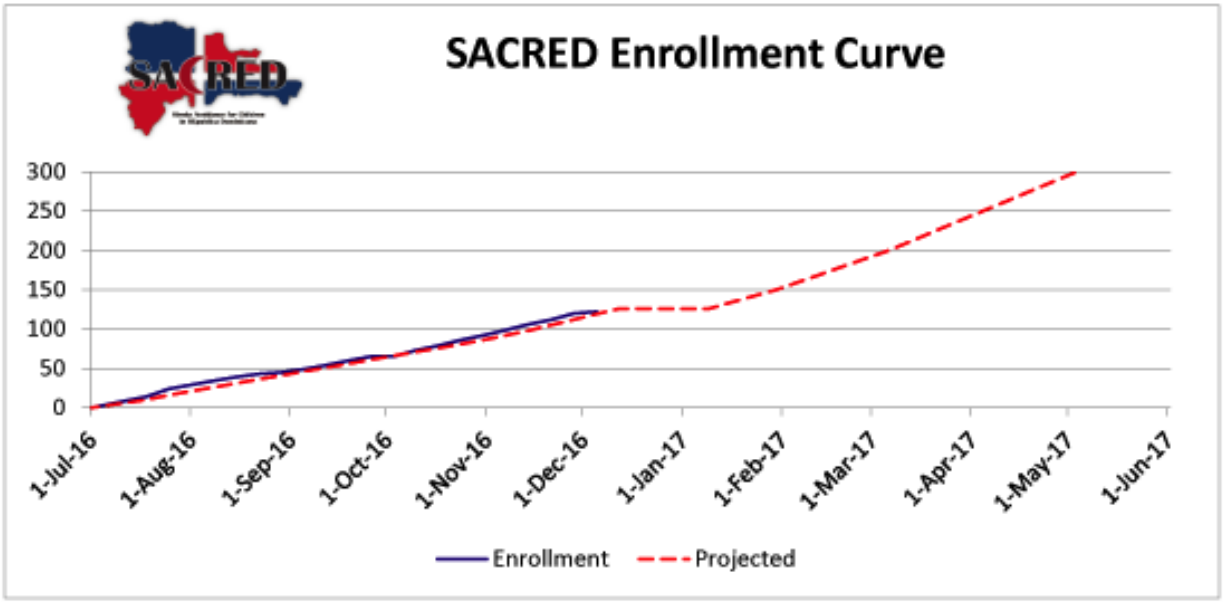
Characteristic		Participants, n
Total enrolled		122
Participants with completed TCD[a] exam		122
TCD exam classification		
	Abnormal	5
	Conditional	29
	Normal	85
	Inadequate	3
	TCD not yet reviewed	0
Hydroxyurea treatment status		
	On hydroxyurea at study entry	22
	Eligible for protocol-directed hydroxyurea	20
	Ineligible for hydroxyurea	0
	Temporarily ineligible for hydroxyurea	1
	Initiated hydroxyurea	17
	Declined hydroxyurea/alternate therapy[b]	8
	Withdrawn after treatment initiation[c]	0
	Currently on hydroxyurea	17
Completed study		0

[a]TCD: transcranial Doppler.

[b]Transfusion due to history of stroke or abnormal TCD.

[c]Includes deceased.

Figure 2. Enrollment curve.



Discussion

Principal Findings

SACRED is the first prospective trial investigating stroke risk among children with SCA in the Dominican Republic, a country where the burden of disease is high. During the first 5 months of the trial, we have observed an excellent rate of patient accrual, which we anticipate will continue, given the reported interest among the local patient population and strong visit adherence within the hydroxyurea treatment group. Our initial data suggest a slightly higher prevalence of conditional, but lower prevalence of abnormal TCD results than anticipated, which could reflect differences in baseline status, previous treatment, or potentially genetics. Data from the United States demonstrate the distribution of TCD velocities to be approximately 70% normal, 15% conditional, 10% abnormal, and 5% inadequate [32,33].

The SACRED trial is also the first study to evaluate the effects of hydroxyurea on decreasing stroke risk in children with SCA living in the Dominican Republic. The potential for using hydroxyurea in this setting is valuable, as it is currently being used for specific clinical indications including vaso-occlusive crises, acute chest syndrome, or repeated priapism. Adding primary stroke prophylaxis to the indications for hydroxyurea could have important implications for reducing the incidence of this devastating clinical event and for preventing its subsequent morbidity and clinical burden. If proven to be beneficial, the goal would be for hydroxyurea to be available nationally at an affordable cost for all at-risk children with SCA. The importance of prospective data regarding its use and safety in the Dominican population are thus crucial to ensure proper accessibility and utilization of this medication.

In addition to the many challenges inherent to conducting an international clinical research trial related to the protocol and data collection, there is a more subtle concern about changing the local standard of care by imposing US-based methods. For example, current clinical practice at the local site is to dose hydroxyurea at 15 mg/kg/day, while SACRED dosing aims to start at approximately 20 mg/kg/day with escalation to MTD. We have explained that our goal is to study the safety and efficacy of higher doses based on published data [37], without suggesting that the site's prior clinical approach was incorrect. Another challenge involves creating dosing regimens with a single 500 mg capsule size, and thus far we have observed exceptional patient compliance even with this alternate dosing schedule.

Conclusion

SACRED is a prospective trial that will yield valuable public health information pertaining to stroke screening and risk among Dominican children with SCA. Further, SACRED will establish local capacity to conduct high-quality research through training and experience with both TCD screening and hydroxyurea therapy among local clinicians. The knowledge and experience gained from SACRED will advance research expertise at the local site and improve clinical care for children with SCA in this country, with the opportunity to expand to other Caribbean nations.

Acknowledgments

The SACRED team would like to thank the participants and their families for their interest, time, and efforts to engage in the trial. The authors also acknowledge the following individuals for their contributions: William Schultz, MHS PA, the SACRED MCC (Rebecca Thompson), and the SACRED DMC (John Boesing, Erica Christensen, Courtney Little, and Justin McAdams). In addition, we would like to acknowledge the many individuals at HIRRC who have accommodated study proceedings at the facility, including the central laboratory, electrophoresis lab, blood bank, and staff at the hematology clinic. Funding is provided by the Cincinnati Children's Research Foundation.

Conflicts of Interest

None declared.

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Abbreviations

ANC: absolute neutrophil count
ARC: absolute reticulocyte count
CBC: complete blood count
CCHMC: Cincinnati Children's Hospital Medical Center
DMC: Data Management Center
HbS: hemoglobin S
HIRRC: Hospital Infantil Robert Reid Cabral
G6PD: glucose-6-phosphate dehydrogenase
MCC: Medical Coordinating Center
MRA: magnetic resonance angiogram
MRI: magnetic resonance imaging
MTD: maximum tolerated dose
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
SACRED: Stroke Avoidance for Children in REpública Dominicana
SCA: sickle cell anemia
STOP: Stroke Prevention Trial in Sickle Cell Anemia
TAMV: time-averaged maximum velocity
TCD: transcranial Doppler

Edited by G Eysenbach; submitted 10.02.17; peer-reviewed by C Thornburg, C Brown, M Reid; comments to author 22.03.17; revised version received 05.04.17; accepted 14.04.17; published 02.06.17.

Please cite as:
Jeste ND, Sánchez LM, Urcuyo GS, Bergés ME, Luden JP, Stuber SE, Latham TS, Mena R, Nieves RM, Ware RE
Stroke Avoidance for Children in REpública Dominicana (SACRED): Protocol for a Prospective Study of Stroke Risk and Hydroxyurea Treatment in Sickle Cell Anemia
JMIR Res Protoc 2017;6(6):e107
URL: http://www.researchprotocols.org/2017/6/e107/
doi:10.2196/resprot.7491
PMID:28576754

Original Paper

A Cloud-Based Virtual Reality App for a Novel Telemindfulness Service: Rationale, Design and Feasibility Evaluation

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Abstract

Background: Worldwide, there has been a marked increase in stress and anxiety, also among patients with traumatic brain injury (TBI). Access to psychology services is limited, with some estimates suggesting that over 50% of sufferers are not accessing the existing services available to them for reasons such as inconvenience, embarrassment, or stigmatization concerns around mental health. Health service providers have increasingly been turning to drug-free therapies, such as mindfulness programs, as complementary treatments.

Objective: Virtual reality (VR) as a new delivery method for meditation-based stress and anxiety reduction therapy offers configurable environments and privacy protection. Our objective was to design a serious learning-meditation environment and to test the feasibility of the developed telemindfulness approach based on cloud technologies.

Methods: We developed a cloud-based system, which consisted of a Web interface for the mindfulness instructor and remote clients, who had 3D VR headsets. The mindfulness instructor could communicate over the Web interface with the participants using the headset. Additionally, the Web app enabled group sessions in virtual rooms, 360-degree videos, and real interactions or standalone meditation. The mindfulness program was designed as an 8-week Mindfulness-Based Stress Reduction course specifically for the developed virtual environments. The program was tested with four employees and four patients with TBI. The effects were measured with psychometric tests, the Mindful Attention Awareness Scale (MAAS) and the Satisfaction With Life Scale (SWLS). Patients also carried out the Mini-Mental State Examination (MMSE). An additional objective evaluation has also been carried out by tracking head motion. Additionally, the power spectrum analyses of similar tasks between sessions were tested.

Results: The patients achieved a higher level of life satisfaction during the study (SWLS: mean 23.0, SD 1.8 vs mean 18.3, SD 3.9) and a slight increase of the MAAS score (mean 3.4, SD 0.6 vs mean 3.3, SD 0.4). Particular insight into the MAAS items revealed that one patient had a lower MAAS score (mean 2.3). Employees showed high MAAS scores (mean 4.3, SD 0.7) and although their SWLS dropped to mean 26, their SWLS was still high (mean 27.3, SD 2.8). The power spectrum showed that the employees had a considerable reduction in high-frequency movements less than 0.34 Hz, particularly with the 360-degree video. As expected, the patients demonstrated a gradual decrease of high-frequency movements while sitting during the mindfulness practices in the virtual environment.

Conclusions: With such a small sample size, it is too early to make any specific conclusions, but the presented results may accelerate the use of innovative technologies and challenge new ideas in research and development in the field of mindfulness/telemindfulness.

(JMIR Res Protoc 2017;6(6):e108) doi:10.2196/resprot.6849

KEYWORDS

Virtual reality; headset; Samsung; psychology; mindfulness; telepsychology; telehealth technology; telemedicine

Introduction

Attention impairment has often been considered a hallmark of mental illness. Attention training is an important part of meditation, and has proven to augment the ability to sustain attention [1]. Mindfulness as a meditation tool has an important role in psychology, self-awareness, and well-being. The authors Brown and Ryan [2] reported that mindfulness over time was related to a reduction in variable mood and stress in patients with cancer. Mindfulness is an internationally recognized therapy that teaches self-awareness, maintaining own thoughts, sensations, feelings, emotions, and appreciation of your living environment [3]. The mindfulness meditation technique may help patients manage potentially negative outcomes and improve well-being by controlling unselfconsciousness (thoughts on failure). Avoiding problems associated with the future, focusing on the present, being "now," and controlling the tracking of time may, in addition to well-being, lead to mindfulness. A person who can achieve such an active and open attention state can control thoughts from a distance, free to judge whether they are good or not [4]. In this context, mindfulness can also be considered an important tool for managing anxiety and stress in patients [2]. Kabat-Zinn [3] designed an 8-week meditation course, Mindfulness-Based Stress Reduction, which provides 2 hours of meditation in a group with additional homework. Mindfulness-Based Stress Reduction has demonstrated that awareness of the mind, unconscious thoughts, feelings, and other emotions positively affect major physiological processes and thus decreases the level of stress-related disorders [4-6].

Anxiety and stress disorders can be related to pressure at work, incurable diseases, or neuromuscular disorders, such as Parkinson disease, light traumatic brain injury (TBI), multiple sclerosis, or other diseases of the muscular or central nervous system. Deficits in executive functions, memory, and learning are often documented after TBI. In addition, at least half of those suffering from TBI experience chronic pain and/or sleep disorders, depression, and substance abuse [7].

A review of the literature shows that neural systems are modifiable networks and changes in the neural structure can occur in adults as a result of training [8]. The study reported on anatomical magnetic resonance imaging (MRI) images from 16 healthy meditation-naïve participants who underwent the 8-week mindfulness program [8]. The results obtained before and after the program suggested that participation in a Mindfulness-Based Stress Reduction course was associated with changes in gray matter concentration in the regions of the brain involved in learning and memory processes, emotion regulation, self-referential processing, and perspective taking.

Early rehabilitation in the acute and subacute phase may be a critical period and a key to effective rehabilitation, especially in TBI [9]. A significant drawback is that patients often stay in hospital for a limited time and are soon discharged for recovery at home. Afterward they can visit an outpatients' clinic. Patients residing close may find the outpatient service convenient, but it could be very inconvenient for those who are in need of ongoing care, are dependent on public transport, or in the worst case do not have access to transport at all. Consequently, external factors such as travel fatigue may hinder the effectiveness of the therapy and, in some, may even increase anxiety and stress. In addition, modern diseases caused by stress and anxiety in the workplace are on the increase, but access to treatment and therapy is usually not possible during working hours [10].

Innovative technologies can ensure real-time communication and data recording/sharing over long distances, even within larger groups of participants [11]. Nowadays, privacy, data security, shyness, and pride are among the most frequent reasons to avoid therapy if a mental disease or neuromuscular disorder is related to work or social status [12].

Some patients prefer to remain anonymous and do not want to reveal their problems, even to colleagues. The sense of "total immersion" created by virtual reality (VR) is an emerging technology that may entirely replace mainstream videoconferencing techniques [13]. These technologies may fulfill patient expectations [14] regarding anonymity and enhance presence [15]. Patients can hide their identify using an avatar and their voices can be disguised. Psychologists and other experts may observe the kinematic changes in motion patterns, gestures, face mimics, and other measurable features [12]. If there is a group, the VR avatars can be synchronized and controlled in real time, using cloud-based technologies. The operator can form groups, deliver individual or group tasks, or lead a private conversation with selected participants. We have developed a technology that is available for home and workplace use, called Realizing Collaborative Virtual Reality for Well-being and Self-Healing (ReCoVR), for which the VR headset is coupled with a mobile phone. The only requirement is a connection to Wi-Fi/4G Internet, plus communication with the cloud server allows remote interaction with other users residing thousands of miles away.

This cloud-based app is used for interaction and communication between a mindfulness expert and participants. Each participant uses a commercially available mobile phone and a simple head-mounted VR headset to join the mindfulness session in the virtual environment (VE). Our main objectives were to design a suitable mindfulness protocol based on Mindfulness-Based Stress Reduction, with tasks in the VE with 360-degree videos, and to test the feasibility of the developed mindfulness/telemindfulness app in a real environment. Additionally, we analyzed head movements during mindfulness sessions to stimulate further initiatives in this research space.

Methods

ReCoVR System Design

The ReCoVR system for mindfulness/telemindfulness has been designed with two options in mind: self-meditation and remote group sessions (Figure 1). The self-meditation was intended for homework or relaxation at home. The remote group sessions option offered each participant to join the virtual group session and attend a guided mindfulness program lead by the instructor/therapist from a remote location. In both cases, participants used VEs and 360-degree video scenes to carry out the mindfulness program in a seated position. Each participant

used a VR headset (head-mounted display), the GearVR (Samsung Electronics Co, Ltd, Seoul, Korea), to interact with the VEs. Various digital objects were designed: VR objects (tables, hourglass), 360-degree videos, music, and natural sounds (birds, wind, waves). The participants set up the options by head movement and pointing on the virtual button. The app for GearVR (tested with Samsung S6, S7, and Note 4 mobile phones) was developed in the Unity3D (Unity Technologies, San Francisco, CA, USA) and built for the Android (tested with Lollipop 5.1 and 6.0 Marshmallow) operating system. The 360-degree videos were recorded at specific locations in County Sligo, Ireland.

Additionally, a server app that hosted the Web-based virtual meeting room (Web user interface [UI]) was developed (Unity3D) and installed on the cloud server (heroku.com). Remote group sessions required a real-time three-dimensional (3D) VR synchronization and also real-time audio-video communication. Our app called a native WebRTC library via Unity3D's plugin mechanism, in addition to the Android Java NDK / JNI mechanism. Therefore, the Web UI required the availability of the WebRTC in the browser (eg, Chrome or Firefox). The application program interface within the app code could access the microphone and video camera, and relay back real-time audio and video. Both the instructor (Web UI) and the participants (GearVRs) acted as clients and connected to the node.js Web server over Hypertext Transfer Protocol to join the group communication session. Node.js configured the session at the OpenTok server (TokBox Inc). Both clients connected to OpenTok over the WebSocket (Transmission Control Protocol) and used the FIWARE Synchronization Generic Enabler (WebTundra, FIWARE) to synchronize 3D VR data. Both clients pushed their audio (and video for the Web UI) streams and subscribed to the streams of other clients, which were transported over peer-to-peer WebRTC (User Datagram Protocol) connections (Figure 1). The participants provided their GearVR/mobile phone's unique ID (a security and privacy feature) once before joining the session and connected to the session using any available Wi-Fi/LTE/3G connection.

Figure 1. The ReCoVR system consists of a cloud server, serving information for the WebGL scenery and synchronization of the data (audio, video, data) between the server and clients. The clients connect to the server as mindfulness experts (using a computer with Web browser) and as mindfulness therapy participants (using Samsung GearVR 3D headset with Wi-Fi/LTE).

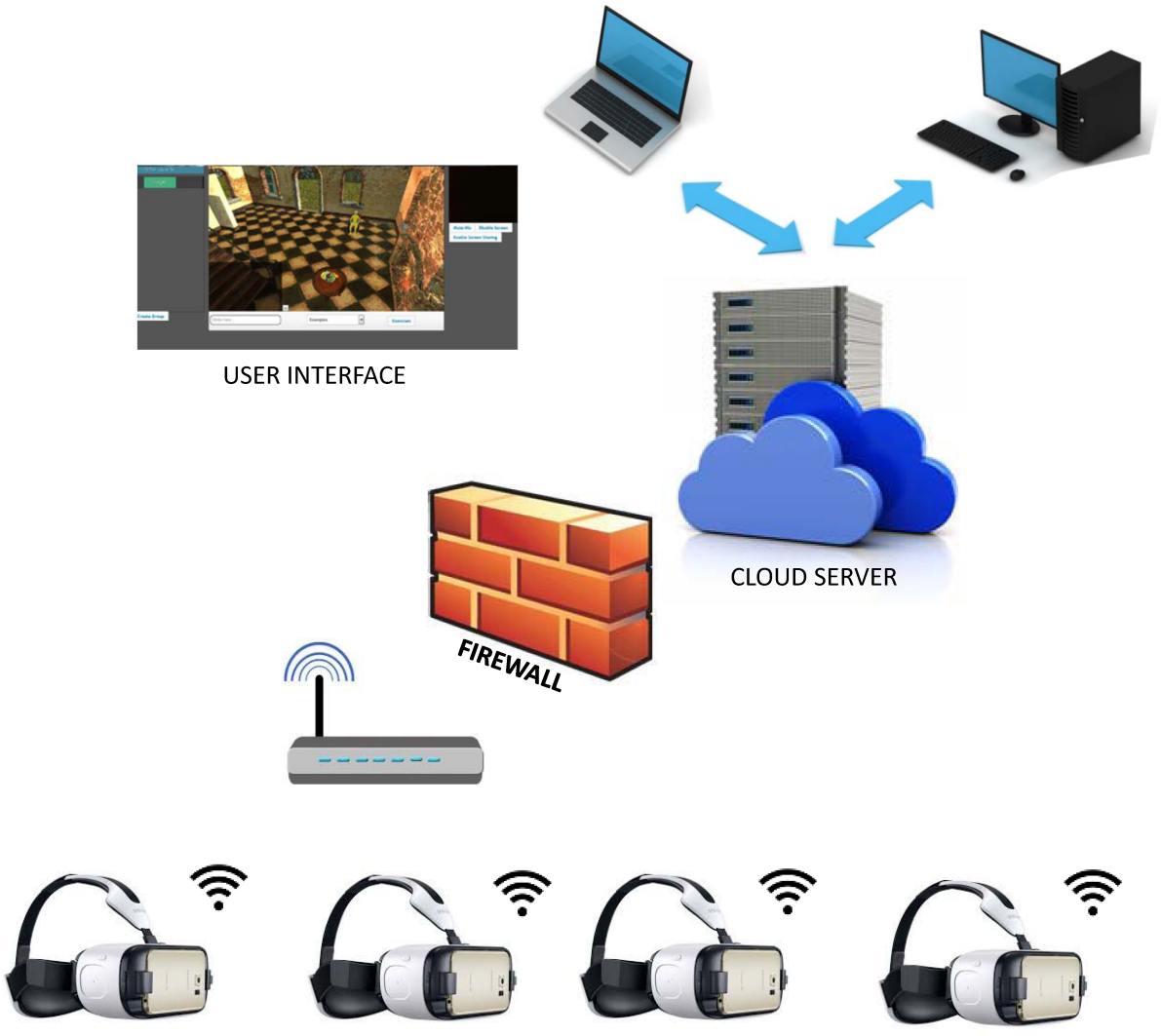
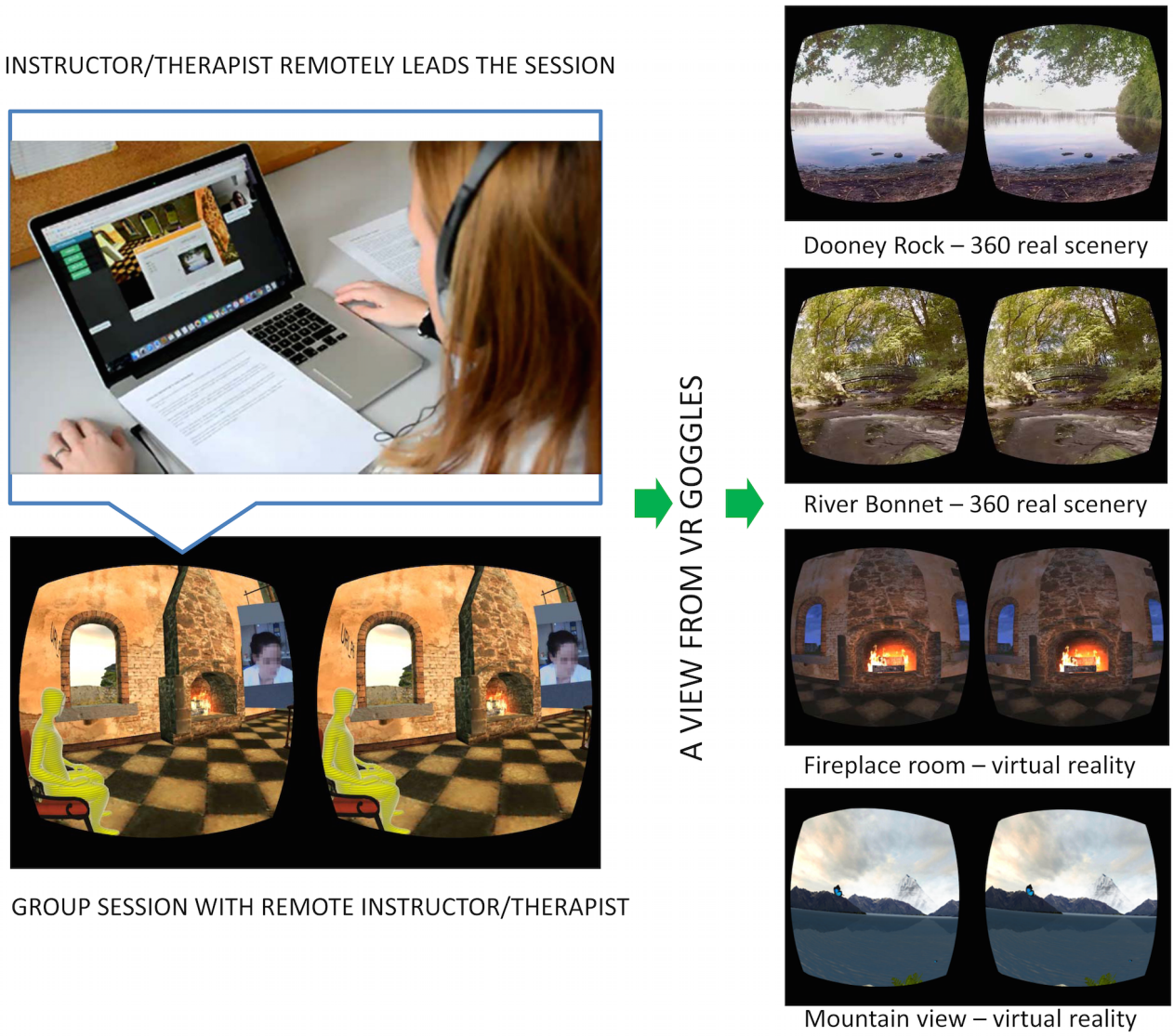


Figure 2. The mindfulness instructor uses the Web interface to manage the group therapy in the virtual room. The Web interface enables video-audio communication with the participants (below left), making subgroups, and assigning tasks (right) for mindfulness sessions. Additionally, the therapist can share documents and lead the session, while everybody can send/receive messages and talk to other group members.



In the self-meditation mode, the user could choose the preferred music, natural sounds, and an environment for mindfulness practice. Four environments were available (Figure 2, right side): two videos recorded in nature with a 360-degree camera (Dooney Rock, a lakeshore in Ireland, and the River Bonnet, a river in Ireland) and two VEs (a dark fireplace room and a bright, wide-open mountain view).

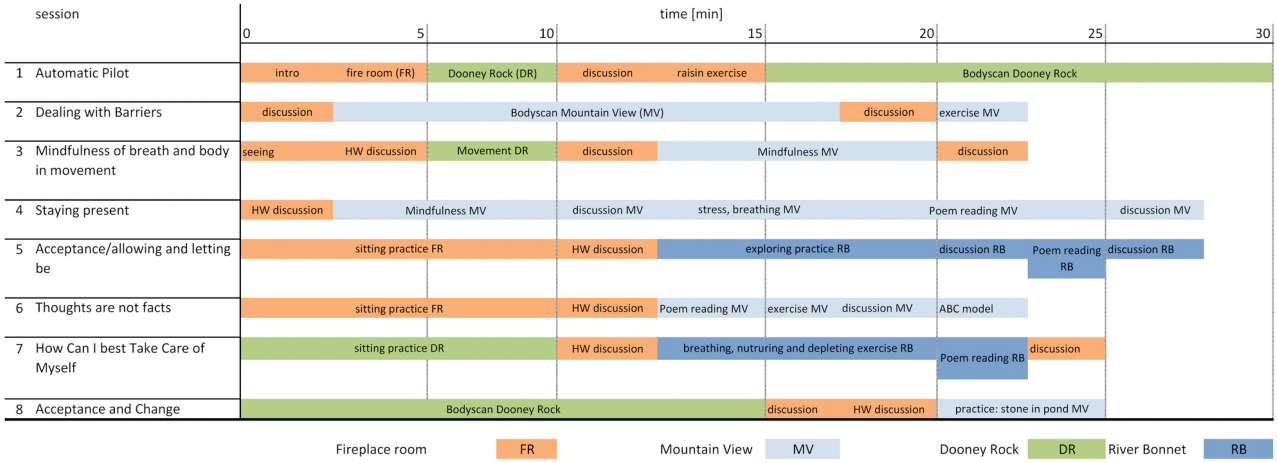
The group session was organized in a virtual room. The user chose to participate in the group session within the 3D VE and received a seat in the virtual fireplace room (Figure 2, lower left). Each participant saw the other participants as avatars and everybody could see the mindfulness instructor on a large screen in the VE. The mindfulness instructor managed the tasks and guided communication over the Web UI (Chrome/Firefox with WebGL support, Figure 2 upper left). The mindfulness instructor saw only the avatars of the participants and a list of their nicknames, whereas the participants saw the mindfulness instructor when his/her video camera was enabled. The mindfulness instructor could also share documents or images, instead of video, or carry out a number of tasks through the Web interface (Figure 2, upper left): (1) video and audio communication with individuals or the entire group, (2) audio communication between the group members, (3) creating additional subgroups of patients, and (4) assign or interrupt exercises to each individual or group. The choice of the exercises and tasks (Dooney Rock, River Bonnet, fireplace room, or mountain view) was determined by the mindfulness program.

Mindfulness Virtual Reality Program

The 3D VR head-mounted devices were not suited for several hours of use, as would be required by the designed Mindfulness-Based Stress Reduction [3,6]. Participants could suffer from headaches or other tolerance issues from overuse of the VR headset. Additionally, it was noted there was a technical limitation in displaying comprehensive VR graphics—overheating of the mobile phone [16]. The overheating of the mobile phone caused unacceptable degradation of graphics and communication quality. Therefore, we limited the sessions to 30 minutes, a time acceptable from the tolerance point of view and the overheating was not excessive. Due to the mobile phone overheating issues [16],

tolerance to VR and technology compliance, we designed a novel mindfulness VR program and split the mindfulness program into sessions (Figure 3). Activities within each session were compliant with the designed VE.

Figure 3. Modified GearVR group mindfulness program.



Session 1: Automatic Pilot

The first session started in the virtual fireplace room with all participants seated as avatars and listening to the mindfulness instructor. In the first five minutes, the instructor presented basic rules about respect, confidentiality, and how to take care of themselves. Afterward, the instructor changed the VE for all participants to Dooney Rock and carried out an exercise called "Stone in the Water," then reverted back to the virtual fireplace room and led the discussion for 3 minutes before continuing with another exercise called "Tasting the Raisin." Session 1 finished with a 15-minute body scan exercise, which was a relaxing meditation. The participants listened and followed the text read by the instructor.

Session 2: Dealing With Barriers

The second session also started in the virtual fireplace room with 3 minutes of discussion followed by the same body scan as in session 1, but this time in the mountain view VE. Afterward, the participants returned to the virtual fireplace room and had a discussion for 3 minutes, before finishing the session back in the mountain view VE with a "thoughts, feelings, and sensations" exercise.

Session 3: Mindfulness of Breath and Body in Movement

The third session also started in the virtual fireplace room with a 3-minute "seeing and hearing awareness" exercise and discussion, followed by a "movement practice" in the Dooney Rock VE. Discussion was led again in the fireplace room for 3 minutes before a "breath and body mindfulness" exercise was carried out in the mountain view VE. The session finished with further discussion in the fireplace room.

Session 4: Staying Present

The fourth session started with 2 minutes of discussion in the fireplace room followed by the following exercises in the mountain view VE: "mindfulness breath, body, sound," "stress reaction/response," "breathing space," and poem reading (*Wild Geese* by Mary Oliver). The session finished with a discussion, this time in the mountain view VE.

Session 5: Acceptance/Allowing and Letting Be

The fifth session started in the fireplace room with a 10-minute sitting exercise, and was followed by a discussion, "exploring difficulty practice," and a poem reading (*Wild Geese* by Mary Oliver), all in the 360-degree video of River Bonnet. The session finished with a discussion, this time in the River Bonnet VE.

Session 6: Thoughts Are not Facts

The sixth session started in the same way as session 5 in the fireplace room and continued in the mountain view VE with a poem reading, a "moods, thoughts, and alternative viewpoints" exercise, and finished with an exercise called the "ABC Model."

Session 7: How Can I Best Take Care of Myself?

The seventh session started with a sitting exercise for 10 minutes, but this time in the Dooney Rock VE. Afterward, the group had a discussion in the fireplace room. The mindfulness therapy continued with a "breathing space" exercise for 3 minutes, "nurturing and depleting" exercise for 5 minutes, and a poem reading (*Summer's Day* by Mary Oliver) for 2 minutes, all in the River Bonnet VE.

Session 8: Acceptance and Change

The final session started with a 15-minute long body scan in the Dooney Rock VE, followed by discussion in the fireplace room for 5 minutes, and finished with "Stone in the Pond," a reflection on what was learned exercise, in the mountain view VE [17].

Psychometric Tests

The modified mindfulness VR program's effect on participants' health and well-being was measured by two psychometric tests: the Satisfaction With Life Scale (SWLS) and Mindful Attention Awareness Scale (MAAS). The SWLS contains five items and factor loadings [18], each scored using a scale from 1 to 7 points. The participants were asked to honestly indicate their agreement with each item by putting the appropriate number in front of the statement: 1=strongly disagree, 2=disagree, 3=slightly disagree, 4=neither agree nor disagree, 5=slightly agree, 6=agree, and 7=strongly agree. The sum of items presented the

SWLS score: 31-35=extremely satisfied, 26-30=satisfied, 21-25=slightly satisfied, 20=neutral, 15-19=slightly dissatisfied, 10-14=dissatisfied, and 5-9=extremely dissatisfied.

The MAAS is a 15-item scale [2] for assessing the characteristics of a disposition toward mindfulness (ie, open or receptive awareness of and attention to what is taking place in the present). The MAAS was validated with college, community, and cancer patient samples [19] and is considered a strong psychometric indicator. The scale contains statements about everyday experience that should be rated honestly on a 6-point scale: 1=almost always, 2=very frequently, 3=somewhat frequently, 4=somewhat infrequently, 5=very infrequently, and 6=almost never. The answers should reflect one's experience rather than what the participant thinks his experience should be. The mean of the 15 items presents the MAAS score; a higher score means a higher level of dispositional mindfulness. The skilled mindfulness instructors can finish the test in less than 10 minutes.

Comparisons (mean, standard deviation) of data assessed with the psychometric tests before the mindfulness sessions, midterm, and after the mindfulness program were carried out separately for employees and patients. Additionally, each participant's results were examined to confirm or drop the deviation from the group mean.

The participants with cognitive disorders also took the Mini-Mental State Examination (MMSE), which is a questionnaire that consists of 30-point questions and is mostly used in clinical settings to measure cognitive impairment. Often it is used by clinicians to screen for dementia [20]. Scores between 25 and 30 are considered normal, 24 and 21 as mild, 20 and 10 as moderate, and less than 10 as severe impairment, according to the National Institute for Health and Care Excellence.

Head Motion Analysis

Head motion was monitored throughout the sessions using the mobile phone's built-in orientation sensor. To avoid singularities due to "gimbal lock," data were supplied in quaternions [21] with a timestamp:

$q=[q_0\ q_1\ q_2\ q_3]^T$

$q=q_1{}^i+q_2{}^j+q_3{}^k+q_4$

The transformation to the Euler angles was carried out similarly to the rotation operation on the selected vector [21], presented as Euler angles $\varepsilon=[\Phi,\theta,\phi]^T$ in the rotation sequence YZX (Figures 4 and 5) (yaw, pitch, roll).

Figure 4. Equation for transformation to the Euler angles.

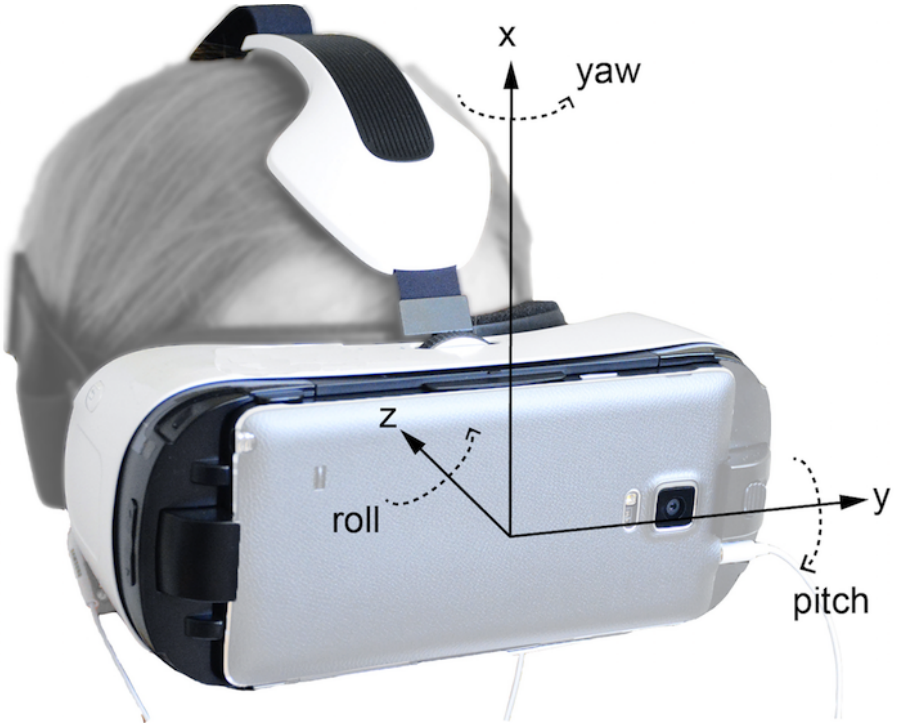
$$\begin{bmatrix} \emptyset \\ \theta \\ \varphi \end{bmatrix} = \begin{bmatrix} \tan^{-1}\left(2(q_1q_0 + q_2q_3).1 - 2(q_1^2 + q_2^2)\right) \\ \sin^{-1}\left(2(q_0q_2 - q_3q_1)\right) \\ \tan^{-1}\left(2(q_0q_3 + q_1q_2).1 - 2(q_2^2 + q_3^2)\right) \end{bmatrix}$$

To avoid limitation to $\pm\pi/2$ with arctan function atan2 function, the SpinCalc package for Matlab (Mathworks Inc, Natick, MA, USA) was used. The obtained signals were preliminary filtered (Butterworth, f=0.5 F_S, F_S=50 Hz) and discontinuities were detected with wavelets [22] and eliminated (using findpeak function of Matlab and own functions for elimination).

During the mindfulness sessions, head motion was constantly monitored. The head motion (roll, pitch, yaw) within the session as well as across the sessions with similar activities (body scan, mindfulness, or poem reading in the same VE) was analyzed using Matlab. The signal analyses were carried out in both the time and frequency domain; the amplitude of the head motion in 3D space and the frequency analysis of the head rotation, yaw. Fast Fourier transform (FFT) was used for spectral analysis of the head motion (yaw) signal (Signal processing Toolbox, Mathworks Inc). In particular, the high frequencies above the cut-off frequency were carefully examined. The FFT specters were compared between the sessions with similar content. The assessment of the section body scan in Dooney Rock from session 1 was compared with the data of the section with the same name from the final session. Further, data obtained from the sitting practice exercises in the fireplace room at the beginning of sessions 5 and 6, and data obtained within session 7, were compared for employees and patients, respectively.

The Euler angles (yaw, pitch, and roll) for similar sections of particular sessions, as previously described, were presented in 3D graphs. Additionally, the motion during the poem reading tasks and River Bonnet virtual worlds were compared between the fifth and sixth sessions. The outcomes were quantitatively evaluated by calculating the entire motion range (the estimated area of the yaw-roll plane curve) of the head for the compared sessions.

Figure 5. Coordinate frame (YZX) attached to the GearVR was defined by Samsung mobile phone and its built-in sensors. The Euler angles yaw, pitch, and roll were used to present head motion.



Participants

The feasibility study involved eight participants in total divided into two groups: four persons of different professions were volunteers/employees of the hospital, aged between 27 and 40 years, with self-reported anxiety and stress. The other four participants were outpatients aged between 24 and 48 years; one patient had a brain tumor and the other three were TBI patients. The medical professionals reported that patients suffered from anxiety and stress due to their uncertainty of the neurorehabilitation program's outcome. These participants were recruited during their visit to the outpatient hospital only if they had matched the inclusion criteria. The inclusion criteria for patients consisted of mild or no cognitive impairment to be able to understand the instructions and follow the program. High diopters were exclusion criteria because the equipment was limited to approximately –3.5 diopters. The headset was not suitable for those with astigmatism and who wore glasses.

The study was approved by the University Rehabilitation Institute's Ethics Committee and all participants signed the written consent that is compliant with the Declaration of Helsinki and European Convention on Human Rights.

Protocol

The feasibility study observed the proposed mindfulness VR program for eight consecutive weeks. The psychometric tests were carried out by the mindfulness instructors before and after the mindfulness sessions (Table 1). Additionally, midterm scoring was performed at week 4. The participants with cognitive disorders were screened for MMSE by a clinical professional at the outpatient hospital. Every week, the participants attended one VR-supported mindfulness group session (Table 1) for approximately 25 minutes, with a 2-minute guided breathing exercise. Additionally, the participants were given instructions for homework: from upright and alert posture, simple breathing and relaxation exercises, and conversations with a friend.

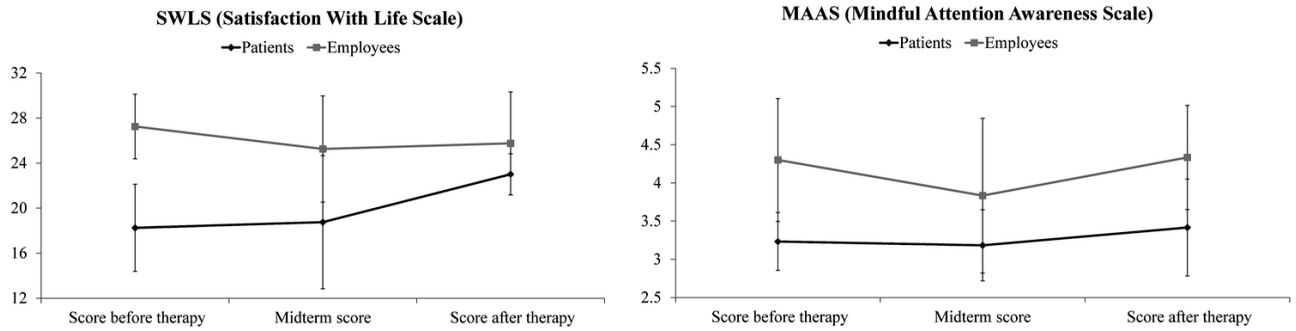
Group sessions were carried out in the hospital environment and under the supervision of the physician/psychologist. Each participant sat in a comfortable chair in a separate room and used the developed software, running on a GearVR, to interact with the group. The equipment was connected to a Wi-Fi or LTE wireless network if the Wi-Fi signal was weak or unavailable to connect to the cloud server (Figure 1). The mindfulness instructor led the sessions remotely from her office. However, before the mindfulness program started all participants were instructed how to properly use the equipment and how to react in case of malfunctioning, etc.

At the end of the mindfulness VR program the participants filled out a short questionnaire; the questionnaire for patients and employees contained questions on the GearVR interface, and the questionnaire for the mindfulness instructor contained questions that related to the Web use interface. Both groups answered voluntarily and evaluated the statements in the questionnaire on a Likert-type scale (1=disagree, 2=light disagree, 3=equal, 4=agree, 5=strongly agree).

Table 1. The mindfulness study protocol.

Week	Tests
1	MAAS [2]; SWLS [18]; MMSE (for patient only)
1-4	25 minutes mindfulness VR per session; 2 minutes breathing exercise per session; 1 session/week for 4 consecutive weeks; homework
4	Psychometric tests
4-8	25 minutes mindfulness VR per session; 2 minutes breathing exercise per session; 1 session/week for 4 consecutive weeks; homework
8	Psychometric tests

Figure 6. The psychometric tests results.



Results

The scores of the SWLS (Figure 6, left) showed that most of the participating patients varied between slightly satisfied and dissatisfied levels of "satisfaction with life" (mean 18.3, SD 3.9) at the beginning of the mindfulness VR program and achieved higher levels of satisfaction with life at the end of the program (mean 23.0, SD 1.8). The participating patients achieved more points on the MAAS (Figure 4, right) at the end of mindfulness VR program (mean 3.4, SD 0.6 vs mean 3.2, SD 0.4). However, a reduction in MAAS points was noticed at the midterm assessment (mean 3.2, SD 0.5). The results in Table 2 reveal that only patient 1's score (MAAS=2.3) deviated the most from the mean value. More detailed insight revealed that items 8 ("I rush through activities without being really attentive to them") and 15 ("I snack without being aware that I'm eating") were unexpectedly lower. However, the patient's SWLS score increased from 16 (slightly dissatisfied) to 21 (slightly satisfied). Only one patient (patient 2) had an MMSE score less than 30; it was 19 when entering the program, but the cognitive score was 26 at midterm and 29 when the program finished. In general, the employees were satisfied with their life (SWLS mean 27.3, SD 2.8), despite their SWLS decreasing slightly to mean 25 (satisfied). However, this deviation was because one employee scored 21 (slightly satisfied). This employee also had a lower MAAS. Generally, the employees kept their aggregate MAAS score at the same level (mean 4.3, SD 0.7) as at the beginning of the mindfulness VR program (mean 4.3, SD 0.8). At the midterm, their MAAS score dropped (mean 3.8, SD 1.0).

Head movements (Figure 7) were analyzed separately for each session and task (VR or 360-degree video) in the 3D space. Practically, we noticed only small amplitudes (less than ±10 degrees) of up and down head movements (pitch) more or less in relation to the frequent glimpses between the instructor view and the surrounding area. Consequently, the rotations of the head (yaw) were of a larger scale (up to ±40 degrees). Roll/tilt of the head was of a larger scale only when movement exercises were requested from the participants (Figure 7, lower right), but most of the time such movements were within a small range (less than ±10 degrees). Also, the rotations of the head were small during the mindfulness sessions in VR (Figure 5, upper right mountain view) and 360-degree videos (Figure 7, Dooney Rock).

In general, the employees rotated their heads left and right to observe the shore of the lake (Figure 8, Dooney Rock, blue solid line). This scenery was obviously very attractive only in session 1, whereas at session 8, there was hardly any head rotation (Figure 8, Dooney Rock, green dotted line). The opposite behavior was shown by the patients. Not only did they rotate their heads, but they also moved up and down to see the trees and the surroundings of the lake during the body scan session in the Dooney Rock 360-degree scenery. However, the range of motion was at least half the mean range shown from the employees (Figure 9, Dooney Rock). The mindfulness practice in the VR mountain view scenery (Figure 8) was rather calm, with slight head rotation (less than ±10 degrees), which was weaker in session 3 than in session 2. The patients (Figure 9, mountain view) performed almost the same action with one exception. In session 2, they also tilted (roll) their head mostly to the left. During sitting in the virtual fireplace room (Figures 8 and 9, fireplace room), both groups—the employees and the patients—rotated their heads left and right to see the virtual fireplace, avatars of the other participants, and from time-to-time the instructor/therapist's video session. The employees reduced their motion curve area by 23% in session 6 compared to session 5, whereas the patients increased their motion curve area by 17% in session 6. However, the patients achieved about half the range of motion of the employees (Figure 8, fireplace room). The head movements during the poem reading in session 5 at the virtual River Bonnet revealed that almost all patients calmed down and some of them also fell asleep for up to 2 minutes

(Figure 9, River Bonnet, blue line). In session 7, they demonstrated head rotation (up to ± 20 degrees) and head tilt (up to ± 10 degrees). It was an opposite result with the employees, who demonstrated head movements in all directions (up to ± 15 degrees) in session 5, but a week later were calmer (motion curve area smaller for 72% with motion up to ± 10 degrees head rotation).

The head rotation during the body scan in the virtual Dooney Rock in session 1 was compared with the recordings of the same task in session 8, in the frequency domain. The employees demonstrated considerable reduction of high-frequency movements greater than 0.34 Hz. However, the observed differences greater than 0.44 Hz assessed in patients were negligible (Figure 10).

Conversely, a comparison of sessions 2 and 3 in the mountain view VE did not show any differences for employees, yet considerable reduction of high frequencies greater than 0.44 Hz for patients (Figure 10, bottom). Additionally, a comparison of the power spectra of the head movements during the sitting mindfulness practices in sessions 5, 6, and 7 also revealed a gradual decrease of high-frequency movements. These turbulent head movements greater than 0.44 Hz had very low amplitudes in session 7. There were practically no changes noticed in sessions with employees. All three sitting practices in the fireplace room VE had the same power spectrum as session 7.

The mindfulness instructor/employees agreed that the UI was not complex, and was easy to use, but did not yet allow enough interventions and should have more options (control buttons) available (Figure 11). The patients also agreed that the game was simple (score 4.6) and that UI was not complex (score 4.4), but they were not convinced whether the users should cooperate and interact with one another within the tasks (Figure 12).

Table 2. The outcomes of the study for each individual participant.

Participant	Before	Midterm	After
Patient			
1			
MAAS	3.3	2.3	2.3
SWLS	16	18	21
2			
MAAS	4.2	4.1	4.8
SWLS	16	11	24
3			
MAAS	3.1	3.4	3.6
SWLS	17	21	22
4			
MAAS	2.4	2.5	3.0
SWLS	24	25	25
Employee			
1			
MAAS	3.3	2.5	3.9
SWLS	28	22	25
2			
MAAS	4.2	3.5	3.7
SWLS	25	22	21
3			
MAAS	4.5	4.5	4.5
SWLS	25	25	25
4			
MAAS	5.2	4.7	5.2
SWLS	31	32	32

Figure 7. Head motion (pitch: head up and down; roll: head tilt left and right; yaw: head rotation left and right) during selected mindfulness program sessions.

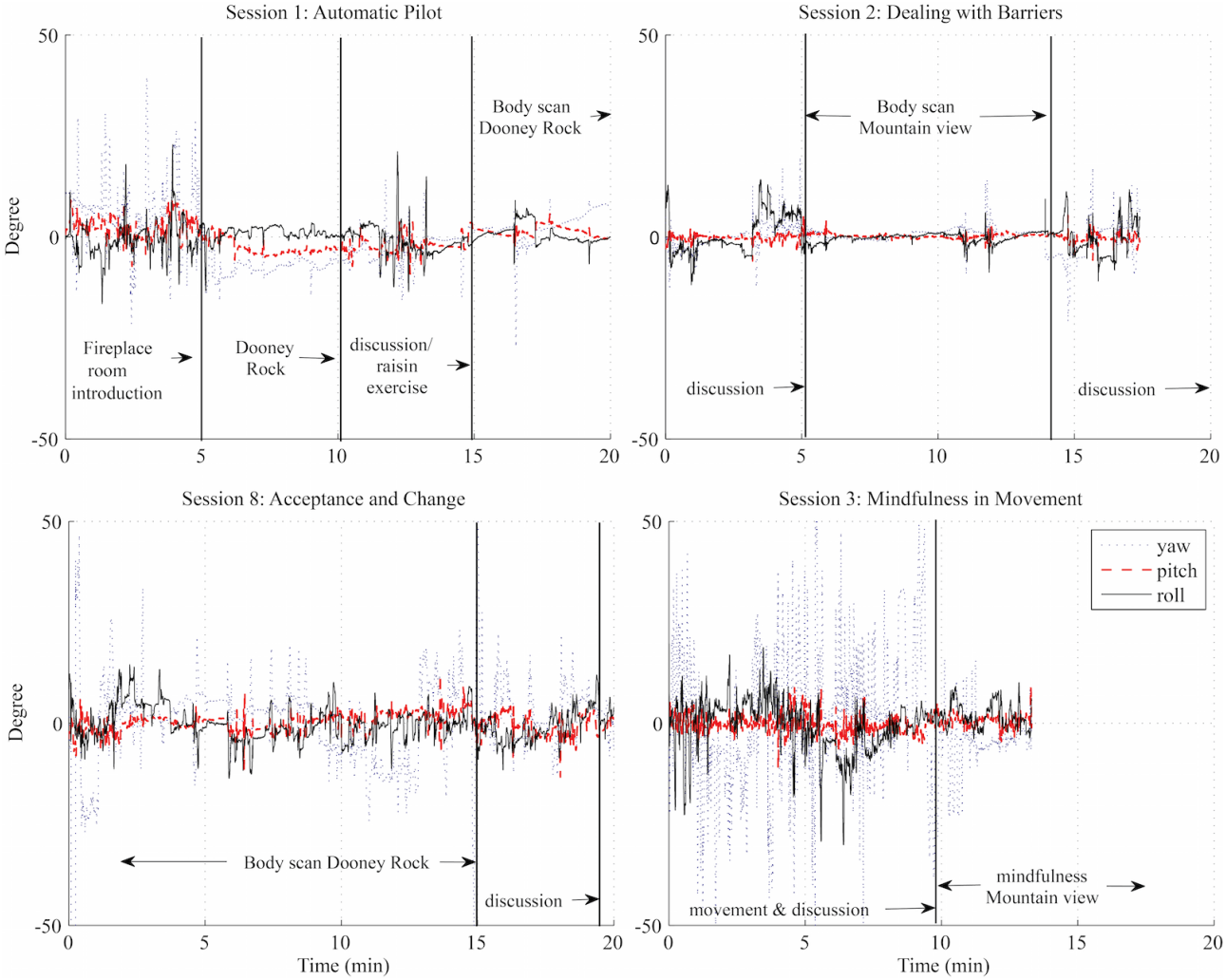


Figure 8. The 3D head movements during various VR and 360-degree video tasks for employees. The solid blue line represents the previous session and the green dotted line the following session, according to the mindfulness program.

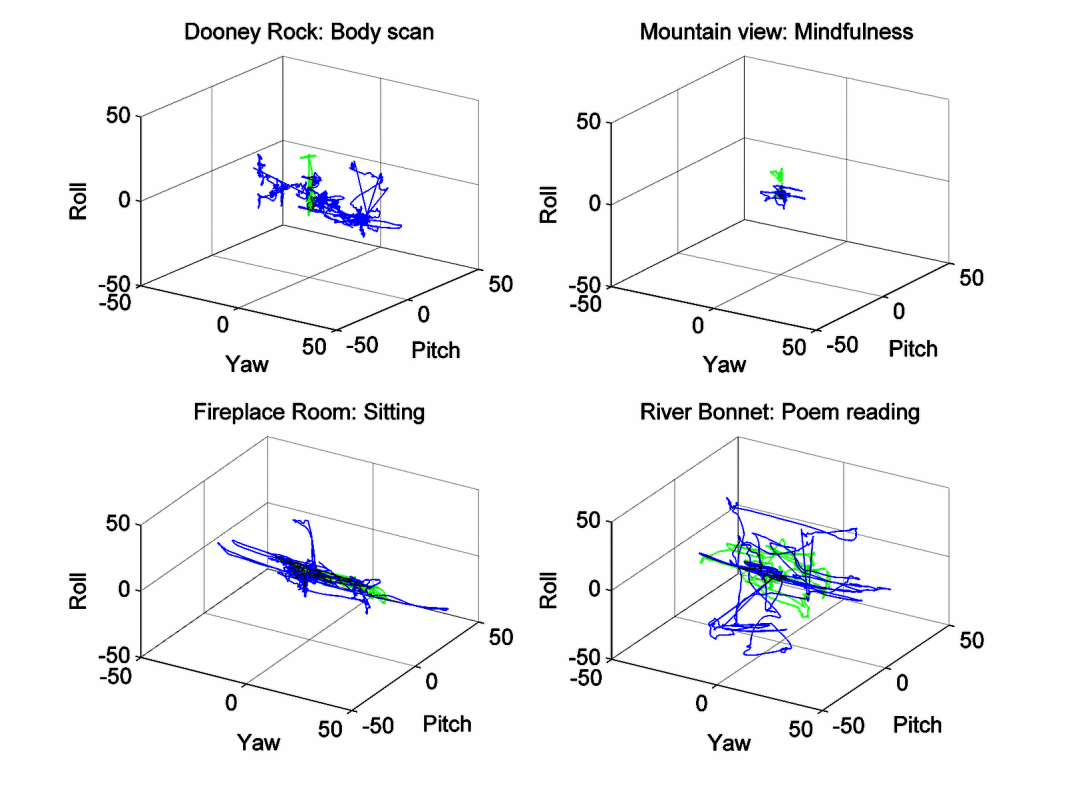


Figure 9. The 3D head movements during various VR and 360-degree video tasks for patients. The solid blue line represents the previous session and the green dotted line the following session, according to the mindfulness program.

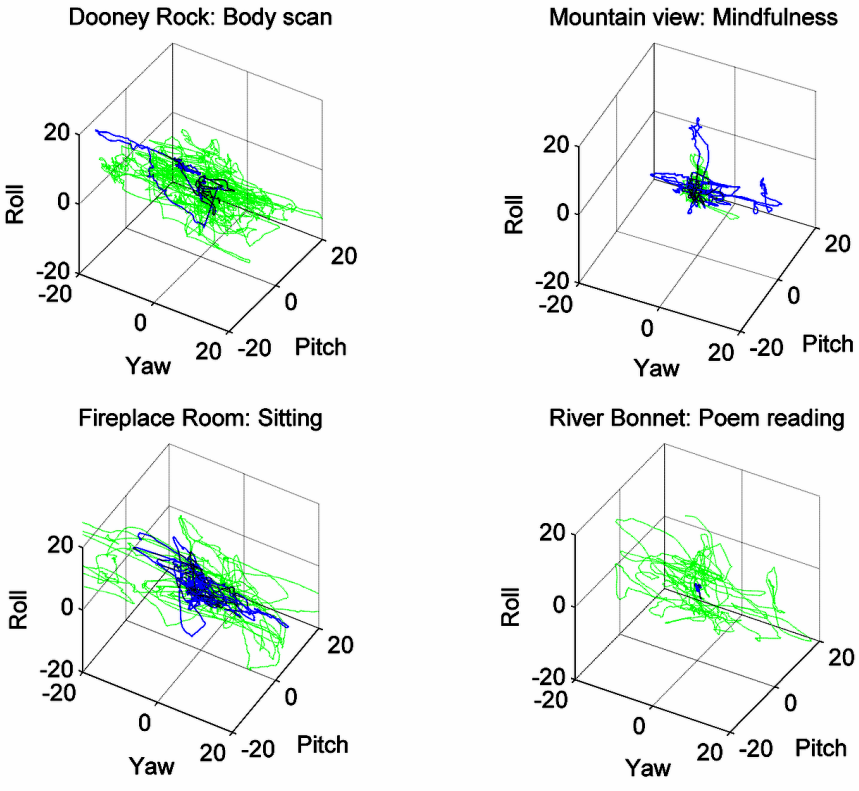


Figure 10. Power spectrum (FFT) of head movements during specific tasks (VR and 360-degree video) of the comparable mindfulness sessions. The patients demonstrated more calm head movements during VR tasks, but the employees did in the 360-degree video tasks.

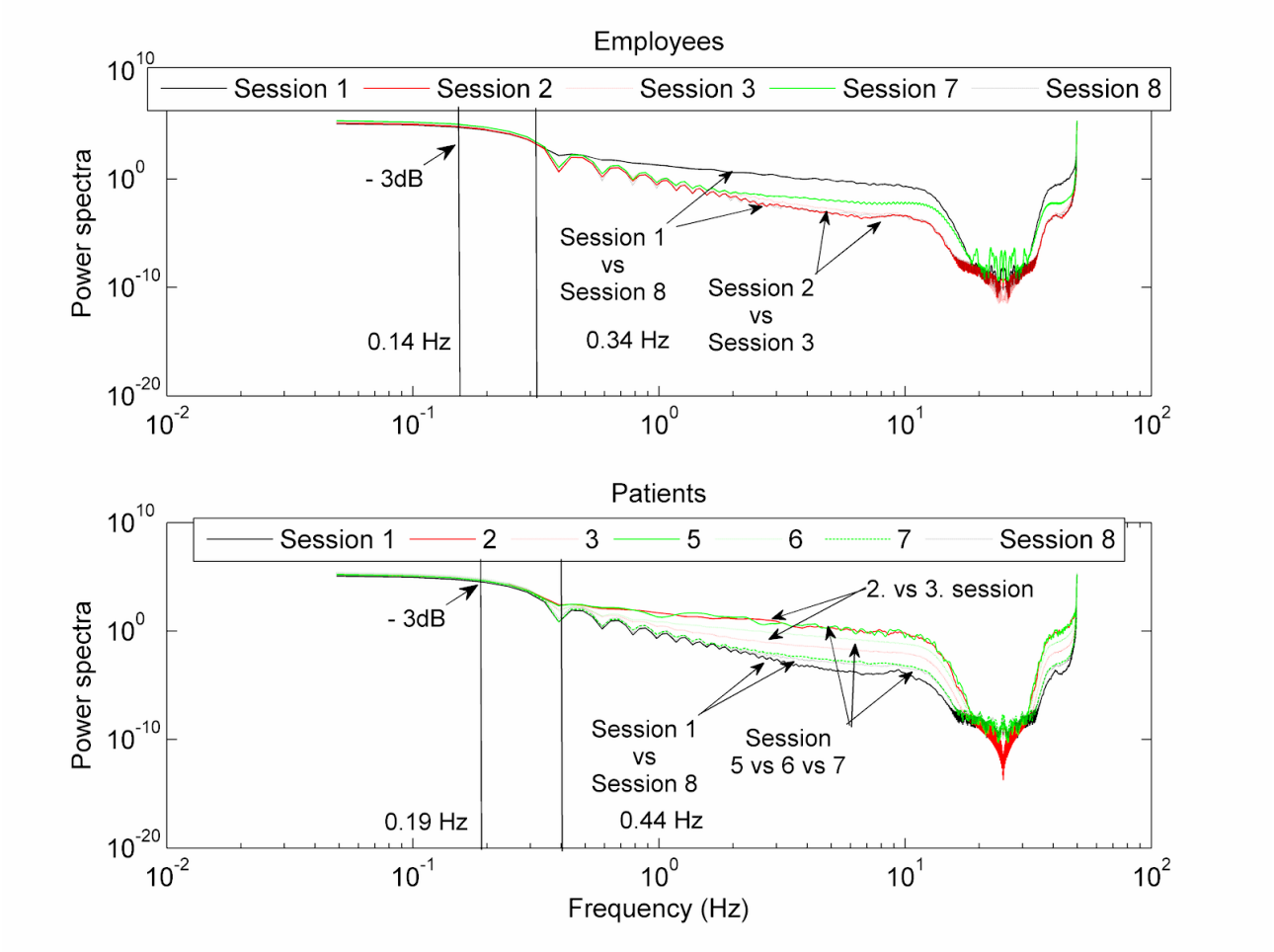


Figure 11. Evaluation of user interface by employees/mindfulness instructor (Likert-style scale, 1=disagree, 2=light disagree, 3=equal, 4=agree, 5=strongly agree).

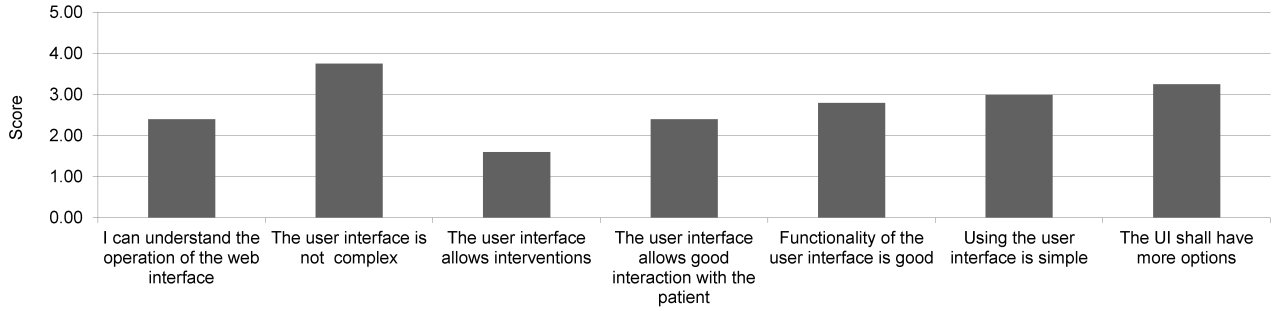
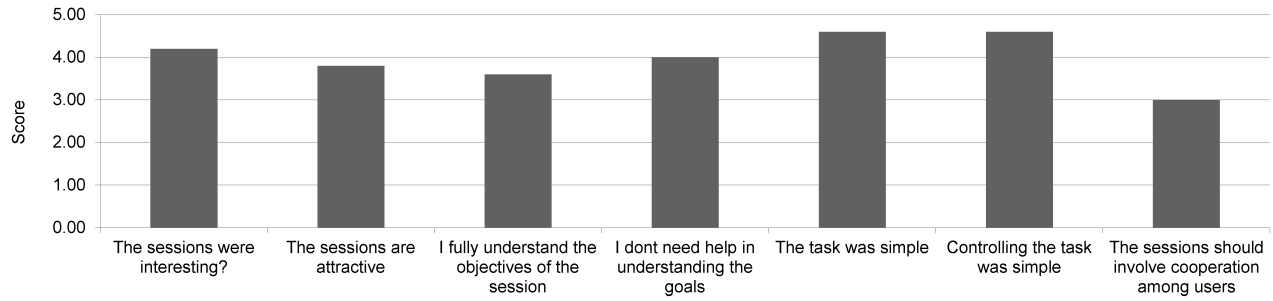


Figure 12. Session/task ratings by patients (Likert-style scale, 1=disagree, 2=light disagree, 3=equal, 4=agree, 5=strongly agree).



Discussion

Patients found the novel technology rather easy to use and not too complex. They were also satisfied with the mindfulness VR program. Much more skeptical were the group of employees, who may not have had such high expectations as the participating patients. They felt that the Web UI should allow more control options, but both groups agreed that the system was not complex and was easy to use. Occasionally, individuals had some difficulties in understanding the goals they were required to achieve. Furthermore, the study revealed how critical the major weakness could be of the proposed system: the mobile phone overheating, a known issue of the Samsung mobile phones [16]. The annoying consequences of the overheating were a gradual loss of graphic detail and disrupted voice communication. In spite of the mobile phones used in the GearVR being the ones with the highest display resolution currently available on the market, the participants were not able to read the text of the documents provided in the virtual room. However, they could follow the photos and video and the text was then read by the instructor.

The employees participating in the study had high SWLS scores. They were all slightly satisfied with their life except one participant, who was extremely satisfied with their life, according to the applied scale. The score has dropped for 2 grades. The MAAS score dropped in the midterm, due to two participants seeming to be preoccupied with their future or job. One of them resolved this problem with the therapy and the overall group score returned slightly above the initial level. The participating patients suffering from neuromuscular diseases or recovering after TBI were all slightly dissatisfied with their life [23]. Yet the therapy resulted in a much higher SWLS end score. Furthermore, the low standard deviation at the end of the therapy pointed to a moderate satisfaction with life from all participants. Additionally, all patients took benefit from the therapy in terms of higher MAAS score, except one participant. A detailed analysis of the scale items revealed that this patient had improved memory function, but still had difficulties focusing on the present. This patient spent most of their time at home and was having family matters. This patient was also the only one with a lower MAAS score at the end of the mindfulness program, although the patient still had a higher SWLS score advancing from “slightly dissatisfied” to a “slightly satisfied” level. In particular, we also noticed that two patients had a slight decrease in MAAS at midterm, which was not surprising. Patients were often confused during the therapy and unsure of the success of the therapy [24]. These promising results at the end of the proposed mindfulness program may indicate reduced subjective pain and changes in the brain [25-27]. However, the authors were also aware of the limitations: several interactions between meditation training and order effect. Yet we had to consider that “no treatment” was not an acceptable option and could be considered as unethical. However, long-term mindfulness practice may lead to emotional stability that may help get over psychological disorders [28]. It was also reported that practicing mindfulness with possible negative emotional events invoked actuation of specific brain regions associated with emotions [29]. The authors reported that the group, in attending mindfulness sessions, showed increased activation in prefrontal regions as identified by functional MRI and, therefore, this group attenuated their emotional arousals more easily compared to the control group [1]. Similar findings on functional reorganization of the brain for focused attention by meditation-related practice were reported by Manna et al [26]. However, we cannot generalize that all types of meditation or mindfulness practice would result in similar clinical effects [30]. For example, the most popular mindfulness program, Mindfulness-Based Stress Reduction, results in positive effects on psychological well-being and causes changes in the gray matter density in certain regions of the brain. Consequently, the learning process, emotion regulation, and self-respect may improve [8].

Mindfulness training involves various interventions for helping people to overcome their fears and neuropsychological disorders. Some of the often-applied mindfulness instructions also invoke contemplative or mindful movements [31]. For example, awareness of sensation used sensations related to autonomic response, even kinematics, and awareness of the present moment (also applied in our mindfulness program) incorporated body movement sensation and breathing but staying in the present moment, not lost in the past or future. Therefore, we directly measured the changes in head motion as a consequence of being present in the VE or 360-degree video providing mindfulness instructions. There have been several theories, as mentioned by Russell and Arcuri [31], trying to explain the potent attentional focus as a consequence of movement and the benefits of mindfulness training on working memory. We are not able to provide enough insight into these mechanisms. Yet our results suggest that patients with neurophysiological and/or neuropsychological disorders increased their head movement amplitudes when they took mindfulness training in the same environment for the second time, although the amplitudes of the movements were in the range of ±20 degrees, approximately half the movement range that employees had. This may be compliant with the suggestions [31,32] that a combination of movements with mindfulness meditation training may engage working memory and be effective in attention focusing. On the contrary, the participating employees in our study reduced their movement amplitudes when they took mindfulness training in the same environment for the second time. The explanation for these differences could be that patients were more instruction dependent, especially awareness of sensation and awareness of the present moment [31], than employees, who after their first relaxation sessions became calm and less interested in the VE. This statement was supported by the movement analysis in the frequency domain. The employees reduced their higher frequency (>0.3 Hz) movement between the first and last session of the body scan exercise in the Dooney Rock environment, whereas there were almost no differences in the movements in the mountain view VE. By contrast, with the patient group we could not find any difference in movements greater than 0.4 Hz when doing the body scan exercise in the Dooney Rock VE, but considerably more differences appeared when sitting in the fireplace room VE. These findings may suggest that the VE can be more effective for patients and 360-degree video for intact persons with mild psychotic problems. However, because

awareness is hard to measure, this could be further confirmed using the clinical and cognitive outcomes [31].

Hereinafter the proposed measurements of head motion could be used as a tool for the assessment of the outcomes of different strategies and mindfulness training instructions. In this way, the mindfulness instructor could alter the instruction set for the next mindfulness sessions. Perhaps a rough estimation of stress reduction, anxiety, or SWLS would have been possible if a correlation with a large group of patients with neuropsychological disorders was demonstrated.

The proposed technical solution for telemindfulness VR has proven to be easy to use and user friendly, and may become useful for remote mindfulness training for various groups of users: hospital patients with neuropsychotic disorders, employees of large enterprises who are not able to leave their offices, and people residing far from the centers where mindfulness is practiced within groups. We managed to demonstrate the feasibility of the proposed solution in a limited group of participants, yet we are aware that some mindfulness training outcomes are extremely difficult to measure [33]. Therefore, the SWLS and MAAS tests were applied and revealed that all but one made a good use of the mindfulness VR training. Additionally, the developed prototype can provide measurable data that may be used in future to predict participant behavior [12] or reaction to specific mindfulness instructions. This leads to further challenges and generation of new ideas in terms of the technology use and research that can continue the development of mindfulness/telemindfulness and its effects from a clinical perspective.

Acknowledgments

The authors would like to acknowledge the coordination and management support from MindMyths Ltd, technical support from PlaySign Ltd, and financial support from FICHe (Future Internet CHallenge for eHealth) under the European Commission Fifth Framework Programme (FP7).

Conflicts of Interest

Mark Roddy is the CEO and the owner of MindMyths Ltd, Ireland.

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Abbreviations

FFT: fast Fourier transform
MAAS: Mindfulness Attention Awareness Scale
MMSE: Mini-Mental State Examination
ReCoVR: Realizing Collaborative Virtual Reality for Well-being and Self-Healing
SWLS: Satisfaction With Life Scale
TBI: traumatic brain injury

UI: user interface
VE: virtual environment
VR: virtual reality

Edited by G Eysenbach; submitted 19.10.16; peer-reviewed by P Gamito, K Cranen, B Ballester; comments to author 28.01.17; revised version received 22.02.17; accepted 05.03.17; published 05.06.17.

Please cite as:
Cikajlo I, Cizman Staba U, Vrhovac S, Larkin F, Roddy M
A Cloud-Based Virtual Reality App for a Novel Telemindfulness Service: Rationale, Design and Feasibility Evaluation
JMIR Res Protoc 2017;6(6):e108
URL: http://www.researchprotocols.org/2017/6/e108/
doi:10.2196/resprot.6849
PMID:28583904

Viewpoint

Phone-Based Interventions in Adolescent Psychiatry: A Perspective and Proof of Concept Pilot Study With a Focus on Depression and Autism

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Abstract

Background: Telemedicine has emerged as an innovative platform to diagnose and treat psychiatric disorders in a cost-effective fashion. Previous studies have laid the functional framework for monitoring and treating child psychiatric disorders electronically using videoconferencing, mobile phones (smartphones), and Web-based apps. However, phone call and text message (short message service, SMS) interventions in adolescent psychiatry are less studied than other electronic platforms. Further investigations on the development of these interventions are needed.

Objective: The aim of this paper was to explore the utility of text message interventions in adolescent psychiatry and describe a user feedback-driven iterative design process for text message systems.

Methods: We developed automated text message interventions using a platform for both depression (EpxDepression) and autism spectrum disorder (ASD; EpxAutism) and conducted 2 pilot studies for each intervention (N=3 and N=6, respectively). The interventions were prescribed by and accessible to the patients' healthcare providers. EpxDepression and EpxAutism utilized an automated system to triage patients into 1 of 3 risk categories based on their text responses and alerted providers directly via phone and an online interface when patients met provider-specified risk criteria. Rapid text-based feedback from participants and interviews with providers allowed for quick iterative cycles to improve interventions.

Results: Patients using EpxDepression had high weekly response rates (100% over 2 to 4 months), but exhibited message fatigue with daily prompts with mean (SD) overall response rates of 66.3% (21.6%) and 64.7% (8.2%) for mood and sleep questionnaires, respectively. In contrast, parents using EpxAutism displayed both high weekly and overall response rates (100% and 85%, respectively, over 1 to 4 months) that did not decay significantly with time. Monthly participant feedback surveys for EpxDepression (7 surveys) and EpxAutism (18 surveys) preliminarily indicated that for both interventions, daily messages constituted the "perfect amount" of contact and that EpxAutism, but not EpxDepression, improved patient communication with providers. Notably, EpxDepression detected thoughts of self-harm in patients before their case managers or caregivers were aware of such ideation.

Conclusions: Text-message interventions in adolescent psychiatry can provide a cost-effective and engaging method to track symptoms, behavior, and ideation over time. Following the collection of pilot data and feedback from providers and patients, larger studies are already underway to validate the clinical utility of EpxDepression and EpxAutism.

Trial Registration: Clinicaltrials.gov NCT03002311; https://clinicaltrials.gov/ct2/show/NCT03002311 (Archived by WebCite at http://www.webcitation.org/6qQtlCIS0)

(JMIR Res Protoc 2017;6(6):e114) doi:10.2196/resprot.7245

KEYWORDS

telemedicine; depression; autistic disorder; mobile applications; text messaging; child; mental health

Introduction

Psychiatric disorders in adolescent populations are extremely common, with a lifetime prevalence estimated up to 46.3% among individuals 13 to 18 years old [1]. As such, mental health disorders among US children have an estimated total annual cost of US $247 billion, with adolescents comprising the majority of these costs [2]. With the advent of mobile technology over the past two decades, there is an increasing need for innovative solutions to deliver inexpensive mental healthcare to our adolescent populations [3,4]. Telepsychiatry is a rapidly evolving field that promises to bridge evidence-based medicine with populations traditionally unable to connect with standard of care [5,6]. While videoconferencing remains the predominant evidence-based platform in telemedicine, phone-based interventions are another accessible and cost-effective method to target a variety of mental health conditions [7]. Here, we discussed the development of provider-prescribed automated text message (short message service, SMS) and phone call interventions for adolescent psychiatric disorders and their potential for improving patient outcomes.

Adolescent Depression

Unipolar major depression (major depressive disorder, MDD) is a psychiatric disorder in which patients suffer at least one major depressive episode that causes significant distress or impairment in daily function, not attributable to mania or other causes [8]. In children between the ages of 10 and 19 years, the 12-month prevalence of major depression is estimated to be 7.5%, increasing significantly through adolescence and rising more quickly than in adults [2,9]. While the prevalence of depressive disorders increases with age for both sexes, adolescent females report a higher average percentage (25%) of depressive symptoms than their male (10%) counterparts [9-12]. Adolescents with depression exhibit decreased productivity in school leading to higher dropout rates, increased anxiety and anger, increased risk of developing other psychiatric and medical illnesses such as substance use disorder, and dramatically increased rates of suicide [13-19]. Currently, the main treatment options for adolescent depression are pharmacotherapy, psychotherapy, or a combination of both [20]. However, due to a high rate of non-compliance and non-responders, continual monitoring is critical to ensure optimal medication titration, decreased suicide rates, remission, and complete functional recovery [21-23]. Because underdiagnosis and undertreatment are common problems in adolescent depression, an annual depression screen using the 9-question Patient Health Questionnaire-9 (PHQ-9) or 2-question PHQ-2 is recommended for all adolescents beginning at the age of 12 until they are 21 [24-26].

Digital platforms are being explored both for screening adolescents at risk for major depression as well as for treatment of major depression in order to minimize costs, improve treatment adherence, optimize pharmacological titration, better track and manage symptoms, side effects, suicidality, and reduce behaviors that increase the risk of relapse. For example, a number of promising computerized cognitive behavioral therapy (cCBT) programs have been implemented in school settings with consistent success [23,24,27-30]. Another example—at-home depression questionnaires administered over mobile devices—have been used to remotely monitor clinically relevant metrics such as the PHQ-9 with remarkable sensitivity and specificity and little variability across race, gender, and age [31,32].

Intriguingly, telemedicine may be uniquely positioned to help depressive adolescents who have consistently responded positively to telemedicine interventions [33-35]. Because depressive adolescents are often reluctant to seek help from social networks, text-based interventions and crisis hotlines have emerged as highly utilized platforms for patients [36]. Adolescents often prefer the convenience, discreteness, increased communication effectiveness, and reduced anxiety associated with texting or talking on the phone compared with in-person evaluations with a physician [37]. Lublin and colleagues at DoSomething, an organization which uses texting to recruit volunteers for social advocacy programs, founded Crisis Text Line in 2013 after seeing an increasing number of teens using the text messaging system to report emotional crises and seek support [38]. Crisis Text Line is now one of the nation's largest crisis text-based hotlines and has processed over 28 million texts to date [39]. As such, text message interventions present a unique intersection between adoptability and utility for detecting depression and even suicidality among adolescents.

Adolescent Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction and the presence of restricted and repetitive patterns of behavior, interests, and activities [8]. Diagnosis, behavioral treatment, and monitoring children with ASD are still in its infancy. Managing ASD is time-intensive and costly and primarily consists of cognitive behavior therapy (CBT) interventions that target development and learning, social skills, and reducing maladaptive behaviors [40]. Although medications are commonly prescribed, they mainly target comorbid conditions and control symptoms, but do not provide treatment for underlying deficits [41]. Importantly, treatment for ASD is most effective when initiated early on and requires frequent follow-up adjustment cycles to be effective. This creates major barriers to care including time, cost, delayed diagnosis, access to specialists, and treatment adherence [42,43]. Aside from questionnaires taken during appointments (which are subject to recall bias), there are limited ways to monitor patient behaviors longitudinally between physician visits [44,45]. As such, there is a critical need to develop inexpensive methods to identify and monitor adolescents with ASD.

Digital platforms have emerged as new ways to improve access to care and better monitor adolescents with ASD. Most interventions have focused predominantly on mobile apps and videoconference services. Services that have been provided remotely through videoconference platforms include: primary evaluations for patients with ASD [46,47], cognitive behavioral interventions [48], and training healthcare professionals in rural areas to provide interventions to children with ASD [49]. Telemedicine systems that provide patients who live in rural areas with access to diagnostics and cCBT are capable of delivering medical care at dramatically reduced costs, without sacrificing diagnostic accuracy, quality, or patient satisfaction [50,51]. Mobile apps are another method for delivering services to children with ASD and their families remotely and electronically [52]. Because mobile apps are point-of-care, physicians can track patients' symptoms with astounding temporal resolution. While these apps have developed more recently than video-based telehealth interventions, apps for surveying high-functioning ASD patients in real-time [53], teaching parents about ASD and treatment options [42], and social skills-building programs [54] already exist.

The benefits of electronic apps are wide-ranging. Enabled by portable computers and mobile devices, sampling methods such as ecological momentary assessment—the process of repeatedly sampling behaviors or experiences in situ in real-time—have been shown to reduce episodic memory decay and recall biases as compared to retrospective questionnaires in patients with high-functioning autism [53]. Moreover, responses on mobile apps reliably matched standard-of-care questionnaires used in clinical practice, making mobile symptom and side-effect tracking a promising option for ASD patients [53]. Though real-time data-driven apps that are used by patients (as opposed to their parents) have the limitation of being applicable primarily to those with high-functioning ASD, the emergence of mobile technologies that cater to patients with ASD that have lower cognitive function continue to prove promising [55].

Phone call and text interventions in adolescent mental health, and especially in adolescent depression and ASD, offer promising ways to improve care, with unique advantages over other digital interventions such as teleconferencing or mobile apps. First, while access to videoconferencing and mobile devices may be limited, phone access is ubiquitous, with more than 90% of the population having access to a mobile phone [56]. Therefore, phone calls and text messaging offer inexpensive alternatives to apps requiring mobile phones with app capabilities (smartphone) or standalone devices. Second, automated texting and calling platforms allow proactive prompting, which improves engagement over mobile apps and allows highly resolved treatment, symptom, and side effect tracking. Third, texting is the primary mode of communication for adolescents, making text-delivered interventions a natural extension of communication with patients' healthcare providers. As such, we set out to build text message interventions for adolescent depression and autism using a patient-centric design process that addressed some of the major pain points in the field.

Methods

Epharmix is an automated texting and calling platform that sends standardized, condition-specific texts or calls to patients or their designated caregivers to track symptoms longitudinally in real-time, provide educational content to patients, and trigger smart alerts to providers when patients report concerning symptoms or behaviors. Two specific interventions for depression and ASD, called EpxDepression and EpxAutism, respectively, have been developed. EpxDepression and EpxAutism were developed using a human-centric design methodology that involved identifying and interviewing seasoned clinicians, research scientists, and biostatisticians in adolescent psychiatry, conducting an extensive literature review, developing optimal questions, alert thresholds, and a clinical decision tree (together known as the "algorithm"), running a small-scale pilot study in a clinically relevant adolescent population as a method for validating algorithm parameters, analyzing data and iterate on the algorithm, using both user feedback and continued research, and interfacing with seasoned clinicians. The unique iteration and development cycle allows rapid, data-driven improvements of the Epharmix systems. Currently, we have run a small pilot for both EpxDepression and EpxAutism and are updating each algorithm based on our results, as well as feedback from providers and patients. These implementations were submitted to the institutional review board (IRB) for review and advised to be pursued as quality improvement (QI) projects. Consent for these studies was received from patients via the Washington University in St Louis "Authorization to utilize unencrypted email/ text messages to communicate protected health information" form as well as verbal consent from patients in accordance with their provider.

EpxDepression

EpxDepression prompts the patient or caregiver for subjective mood and sleep ratings on a 10-point rating scale every day, and sends a text-based modified PHQ-9 every 2 weeks or month, depending on the provider's assessment of the patient (Figure 1). While the modified PHQ-9 is administered through a text message platform as opposed to in-person, its scoring function was adapted to give an equivalent score to the original PHQ-9. Depending on the patient's mood, PHQ-9 score, and self-harm ideation (a positive response on the last question of the PHQ-9), the patient is triaged into a red-yellow-green hierarchy. Patients who are scored as high-risk (red) are automatically reported to the care team. Importantly, patients who report self-harm behavior are automatically directed to a suicide help-line, crisis manager, or entrusted caregiver (Figure 1).

In our initial pilot study with EpxDepression, our primary aim was to assess patient engagement with an automated texting platform. We enrolled 3 adolescent patients with MDD in EpxDepression and assessed their weekly response rates to the mood, sleep, and PHQ-9 prompts. A weekly response is defined as having answered at least 1 question during the week for the associated prompt. The frequency of the PHQ-9 questionnaire was determined by the specific program the patient was placed in (once every 2 weeks or once a month), while the mood and sleep questions were asked daily. The duration of enrollment

varied on a case-by-case basis, spanning anywhere from 2 to 4 months.

EpxAutism

In our initial pilot with EpxAutism, 6 adolescent patients with ASD and their parents were enrolled in the study. The duration of enrollment varied on a case-by-case basis, spanning anywhere from 18 to 110 days. EpxAutism prompted each patient's caregiver daily for the patient's quality of life, the number of meltdowns the patient has had in the last 24 hours, and the duration of the longest meltdown (Figure 2). The system synthesized data received through text responses for each individual and triaged patients into 1 of 3 risk categories including red (high risk), yellow (moderate risk), and green (low risk) based on a change in meltdown frequency and duration as set by their provider and sent alerts to providers upon recognizing significant upward deviations in recorded meltdowns.

The aim of EpxAutism was to improve a provider's ability to monitor patient behavior and symptoms between visits, foster communication between the patient and provider, and improve survey compliance and health outcomes for the patient. Our primary outcome was weekly response rates, but we were also interested in overall response rates, behavioral metrics reported by the caregivers, and feedback from parents using the system. Similar to our pilot study with EpxDepression, weekly response was defined as having answered at least 1 question during the week for the associated prompt, and overall response rate was defined as the number of prompts answered divided by the number of prompts sent to the parent.

Figure 1. EpxDepression automated text message algorithm.

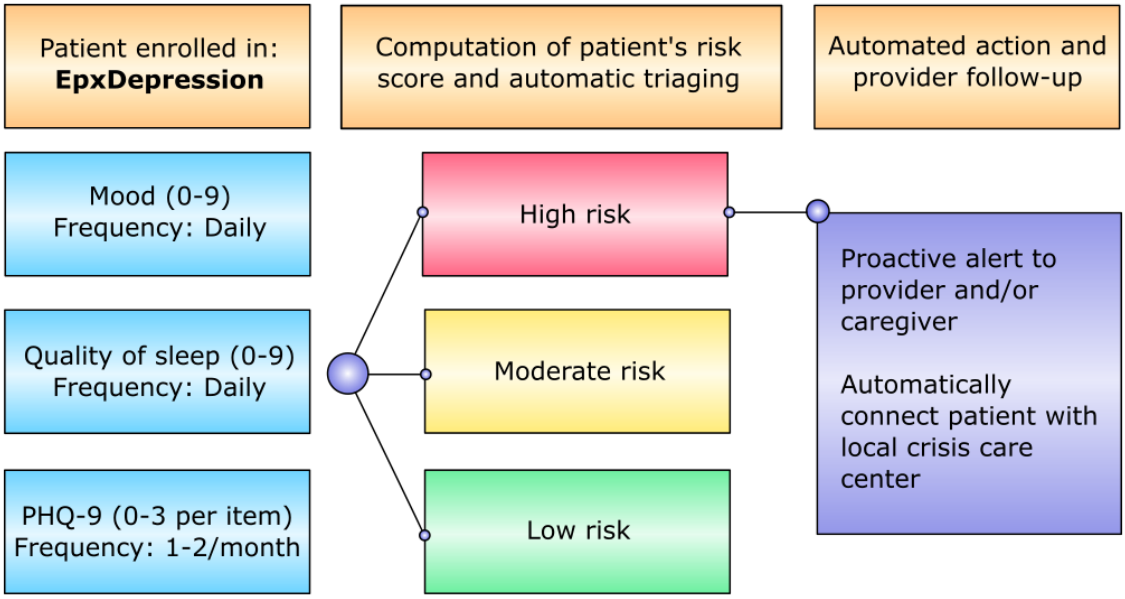
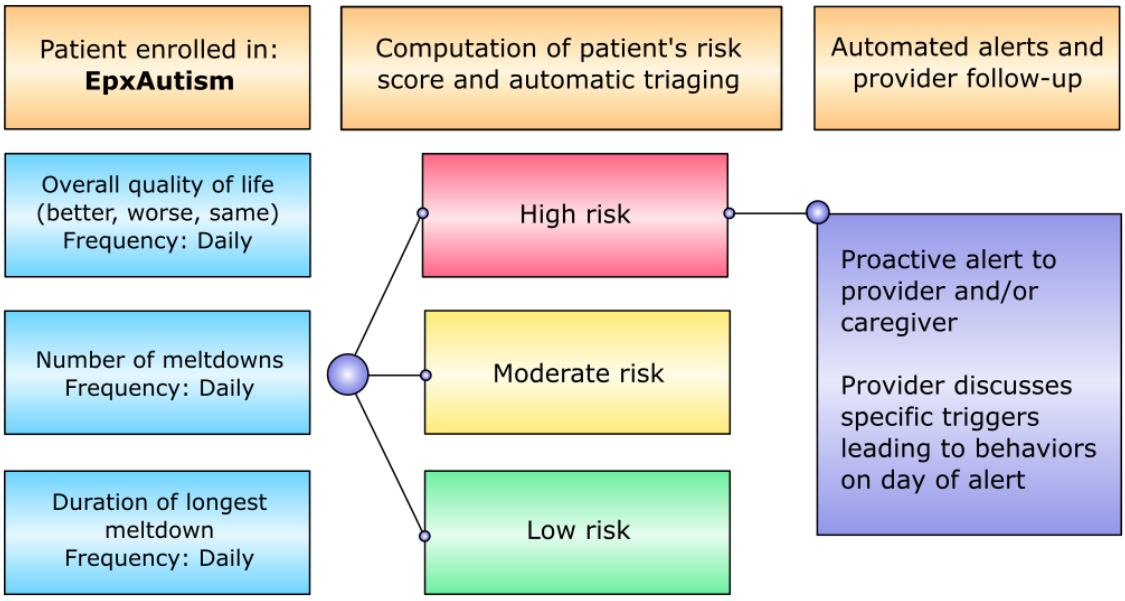


Figure 2. EpxAutism automated text message algorithm.



Textbox 1. Survey prompts.

Prompt
• Communication: On a scale of 1 to 9, do you think this service improved communication with your doctor? (1 = significantly worsened, 5 = no change, 9 = significantly improved).
• Frequency: On a scale of 1 to 9, how do you feel about the number of messages you received through our service? (1 = too few, 5 = perfect amount, 9 = too many).
• Improvement: How could we make this service better? Feel free to write as much as you would like.
• Positive Comment: What did you like about this service? Feel free to write as much as you would like.

User Feedback

Users were sent monthly surveys through text messages which asked for subjective feedback on the EpxDepression or EpxAutism systems. Deidentified survey data was used frequently to iterate on specific questions, timing of messages, and triaging methodology. Prompts within the survey are shown in Textbox 1.

Results

EpxDepression

We found that with the mood, sleep, and PHQ-9 questionnaires, patients maintained a 100% weekly response rate during their enrollment in the study, indicating that no patients were lost to follow-up. However, overall response rates for mood and sleep, defined as the percentage of questionnaires completed for mood, sleep, or PHQ-9 whenever prompted, was markedly lower (Figure 3). The mean (SD) daily response rate for mood was 66.3% (21.6%) and sleep was 64.7% (8.2%). The response rates decreased over time, with the sleep prompt having lower response rates and greater decay than the mood prompt from the outset (Figure 3). Our preliminary data suggested that adolescents with MDD engaged with prompts on a weekly basis in a robust fashion, but underwent message fatigue with daily prompts. A larger study will be necessary to confirm our findings.

While our primary outcome was weekly response rates over time, we wanted to determine whether self-reported mood or sleep ratings could predict a patient's PHQ-9 score as suggested in other studies [34]. We averaged each patient's mood or sleep ratings leading up to a PHQ-9 prompt, and regressed these averages against the patient's PHQ-9 score for that time point. Based on our data, mood (R^2=.20, P=.12) and sleep (R^2=.14, P=.26) were not significantly correlated to the PHQ-9 score, although both trended toward a negative correlation as might be expected (Figure 4). Self-reported mood ratings were positively correlated with sleep ratings (R^2=.61, P=.005) and consistent with the literature (Figure 4). Due to the small sample size, these results are suggestive; future studies with a larger sample size will be needed to determine whether self-reported mood and sleep ratings can predict self-reported PHQ-9 scores collected through automated text-messaging.

Despite the small sample size, the EpxDepression module has already made a tangible impact in the lives of our patients. EpxDepression is programmed to automatically alert the patient's care provider if the patient reports a positive response to the suicidal ideation question (question 9) on the PHQ-9 survey. In the 2 patients who scored positively on this question, EpxDepression detected and alerted the patients' care providers of the patients' self-harm ideations, even before the case manager was aware that the patient was having these thoughts. The case manager was able to follow-up with each patient and confirm that the patient was having suicidal ideation, and care was modified appropriately. These instances demonstrated that patients with MDD in our study were willing to disclose suicidal ideation through text-messaging before telling their case manager or families in person.

From adolescent patients enrolled in EpxDepression, 7 feedback surveys were completed where users answered a valid response for at least 1 of the prompts. From the small sample size, users indicated that the number of messages received was the "perfect amount" (median=5) where 1 was too few, 5 was the perfect amount, and 10 was too many. There was no improvement in communication between patient and provider attributed to the intervention, as observed by a mean value of 5, where 1 indicated significantly worsened, 5 indicated no change, and 9 indicated significantly improved. Positive feedback commonly included improved feeling of support and contact between patient and provider:

> *"Knowing my Dr [sic] is in contact and aware of my answers."*
>
> *"I like the daily contact."*
>
> *"Service gave me feeling of daily contact with my Dr [sic]."*

Despite indicating that there may not have been any improvement in communication with providers, no patient provided any negative feedback based on survey results. Most feedback included confirmation of "service works fine" or "service is great" when queried for areas of improvement.

Figure 3. EpxDepression patient overall response rates.

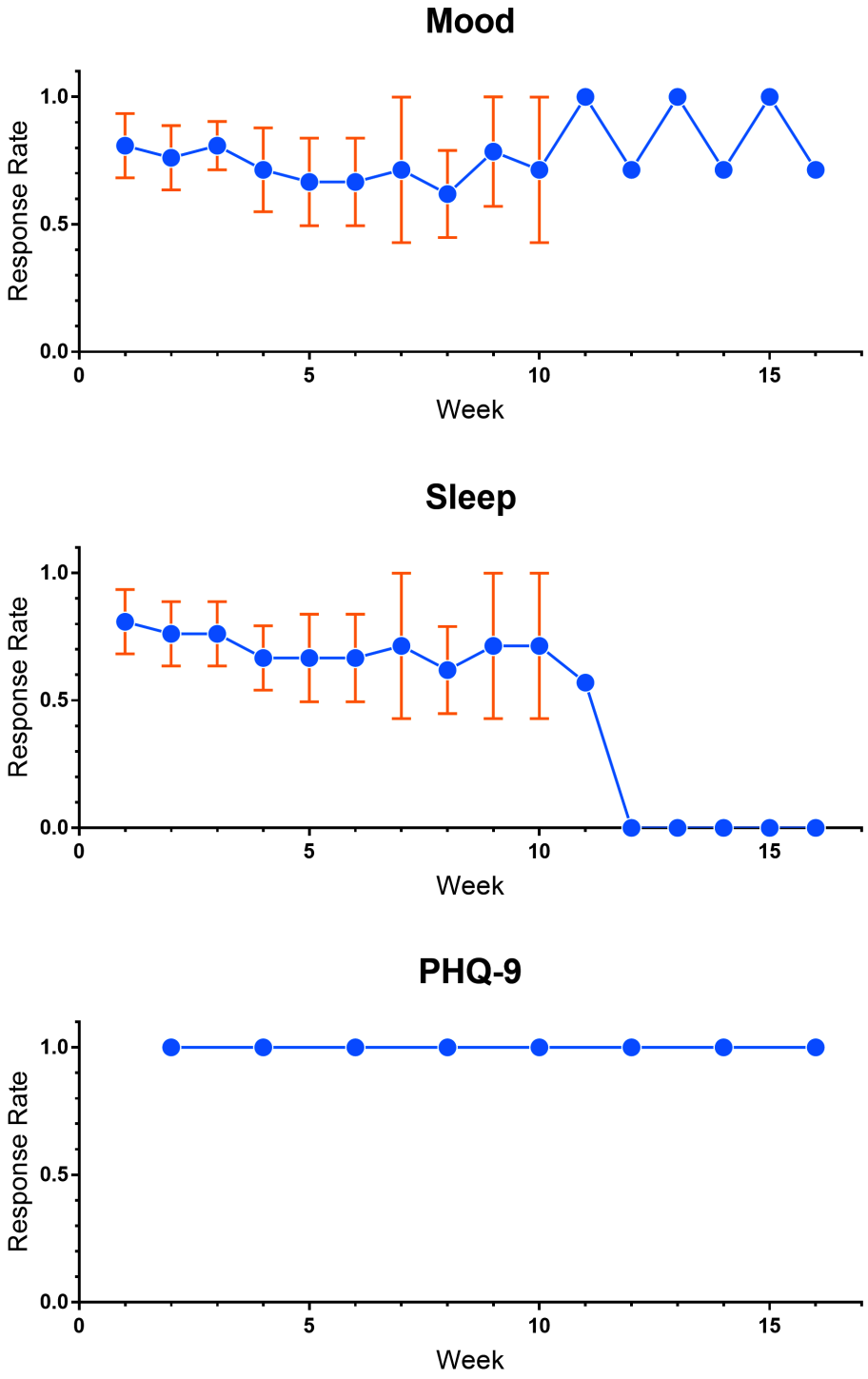
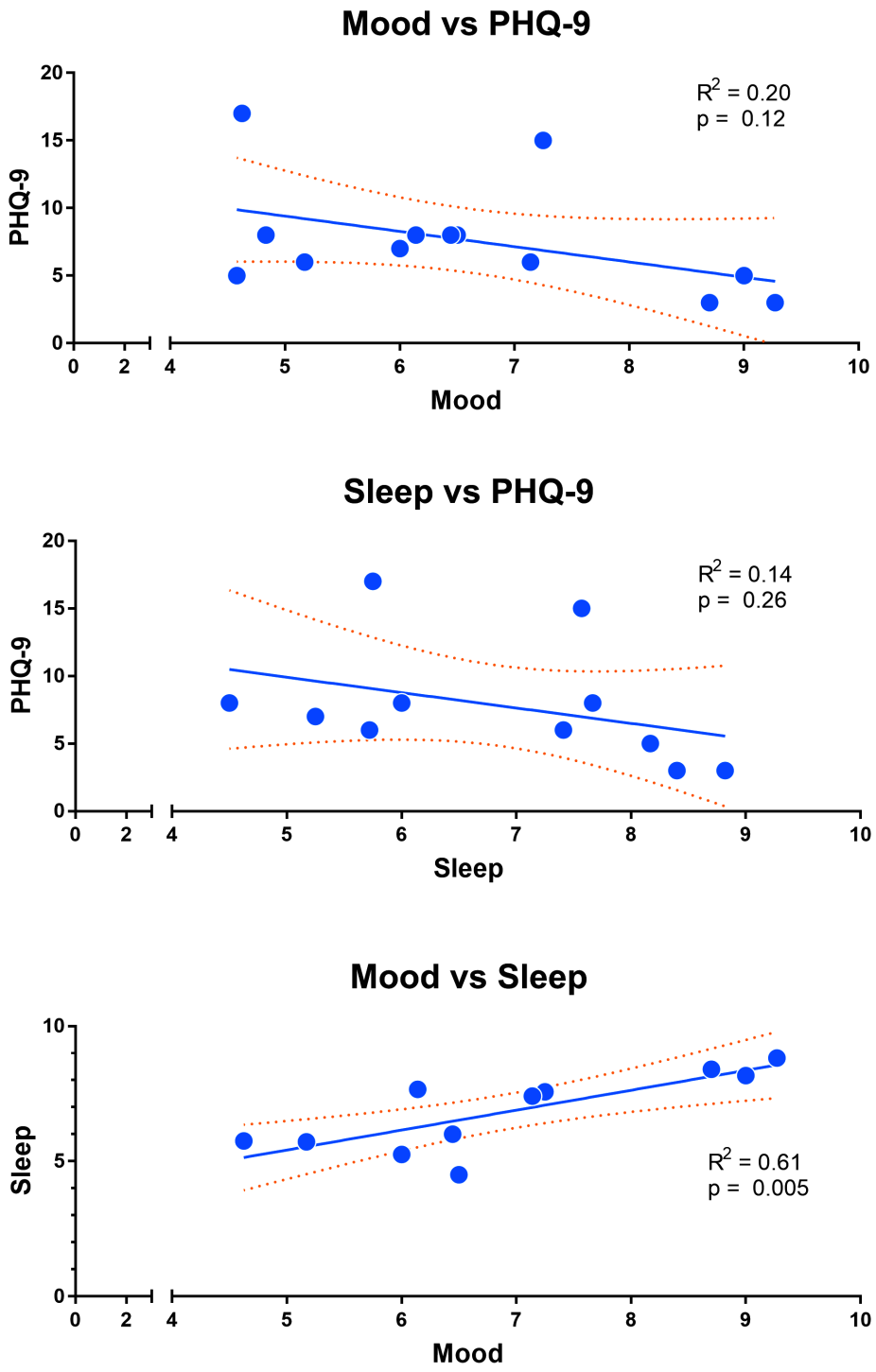


Figure 4. EpxDepression correlations between outcomes.



EpxAutism

The weekly response rate for parents using EpxAutism was 100%, indicating a robust and prolonged enrollment in the system that did not decay with time. Remarkably, the mean (SD) overall response rate even with daily questions was 85% (29.1%) (Figure 5). Unlike with mood and sleep prompts in EpxDepression, there was no significant difference between overall response rates between individual prompts in EpxAutism. High engagement rates were maintained throughout the duration of the pilot. Our data suggested that EpxAutism is an engaging system for caregivers with children with ASD and may be used to better track concerning symptoms and behaviors on a daily basis.

Participants enrolled in EpxAutism completed 18 surveys in which a valid response for at least 1 of the prompts was submitted. When queried about communication between patient

and providers, users responded to "On a scale of 1 to 9, do you think this service improved communication with your doctor?" On this scale, 1 indicated significantly worsened, 5 indicated no change, and 9 indicated significantly improved. The determined median score of 7 indicated an improvement in communication from use of EpxAutism.

In terms of frequency of text messages, parents received 3 prompts daily about their child's behavior. When surveyed, parents responded to "On a scale of 1 to 9, how do you feel about the number of messages you received through our service? On this scale, 1 indicated too few, 5 indicated the perfect amount, and 9 indicated too many. Patients reported a median response value of 5.

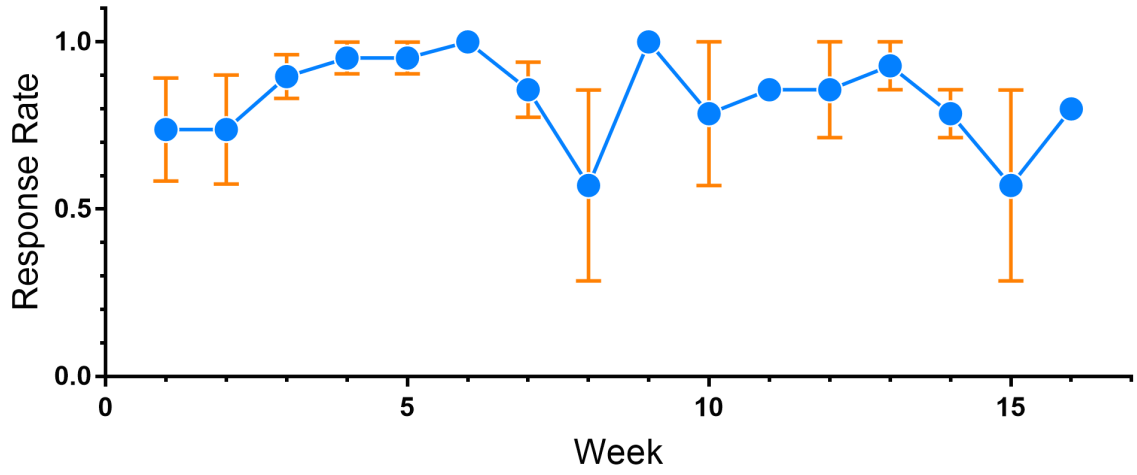
Positive comments often reflected the importance of daily communication and feeling connected with their provider:

> *"Daily contact and reporting is what we need to help identify issues and help our son."*
>
> *"More communication is better and daily tracking is needed. Thanks."*
>
> *"The service is great. I appreciate all that [provider] has done to teach [my son] to better control himself and he has helped me with ways to help my son as well. I liked having a record of [my son's] improvement. It seemed to help [my son] knowing [provider] was checking up daily to see how well he was doing."*

Areas of improvement almost universally revolved around caregiver desire to input more information to providers:

> *"Be able to provide [sic] a few more details."*
>
> *"I think a comment space would be nice."*
>
> *"Allow for additional comments about behaviors...I think it would be helpful to include additional commentary about time of day or specific issues."*

Figure 5. EpxAutism patient overall response rate.



Discussion

Principal Findings

While pharmacology and psychotherapy have made remarkable progress in addressing patients with adolescent depression and ASD, there exists a dearth of reliable methods to track symptoms over time, monitor behavior, and prevent suicidal behaviors. New ways to leverage mobile technology continue to augment traditional patient monitoring and treatment options. Electronic office visits and CBT sessions have robust literature supporting their efficacy, expanded access to care, time efficiency, and satisfaction among providers and patients alike [5,32,51]. However, there is a much smaller body of literature describing the utility and efficacy of mobile apps, phone call platforms, and text message interventions in adolescent depression and, especially, ASD. Overall, the literature supports mobile platforms as promising ways to deliver and improve adherence to CBT, track symptoms, monitor behavior, and engage patients. Because landline and texting are ubiquitous forms of communication, especially in adolescent populations, these platforms offer a unique angle to improve patient care.

In order to explore text message interventions in adolescent populations with depression and ASD, we developed 2 automated text message systems called EpxDepression and EpxAutism. In our initial pilot with EpxDepression, weekly response rates were very high, whereas overall response rates on a prompt-by-prompt basis suffered from message fatigue. Because only the daily mood and sleep prompts showed signal decay with time, our data suggested that adolescent patients with depression found daily questions about their mood and sleep tiresome, unhelpful to their care, or were simply more engaged with questions asked on the PHQ-9. Patient feedback indicated that frequency of total prompts was satisfactory with no complaints about the mood or sleep questions, suggesting a difference in engagement to these questions attributed to the lack of perceived usefulness or patient interest. As such, we are currently modifying the mood and sleep questions within the EpxDepression algorithm.

Previous studies have shown that subjective mood ratings submitted over the phone correlate with in-person PHQ-9 scores [34]. In our small pilot with EpxDepression, we failed to find a significant correlation between recent mood or sleep scores

and PHQ-9 scores. However, given our small sample size and the exploratory nature of this pilot, further investigation will be necessary to determine whether self-reported subjective mood and sleep ratings can predict PHQ-9 scores. In addition, due to the correlation we found between mood and sleep ratings, we plan on incorporating a split testing method for EpxDepression and analyzing response rates with or without sleep prompts, which may help alleviate message fatigue without losing significant amounts of predictive or clinical information.

Perhaps the most illuminating result from the EpxDepression pilot was the capability for a text-based PHQ-9 questionnaire to detect self harm ideation, even before parents and case managers were made aware. Our data is in line with the spontaneous success of text-based hotlines, and may reveal the willingness of adolescents to disclose more personal information about their mental health to electronic devices, which feel less judgmental than face-to-face disclosure [37-39,57]. As such, an inexpensive, proactive, phone-based depression monitoring platform such as EpxDepression may be a valuable tool not only to track mood, sleep, and depressive symptoms between visits, but also to detect suicidal ideation and even prevent suicidal events. We are currently piloting the second iteration of EpxDepression in a larger study to confirm our preliminary findings reported in this pilot.

In our initial pilot with EpxAutism, we found remarkably high weekly and overall response rates that did not appear to decay significantly with time. Though larger studies are needed, if this trend holds true, the difference in overall response rates between our pilot with EpxAutism and our pilot with EpxDepression may be attributed to a difference in user motivation, demographics, or a perceived benefit of each question on the user's care. Of note, the patient population was particularly different between studies, where users enrolled in EpxAutism were caregivers responsible for their children's health, whereas EpxDepression was used by adolescents themselves. Future interventions for EpxDepression may be able to utilize the increased caregiver engagement to build complementary monitoring systems, such as a depression intervention for the adolescent patient involving the patient's parents or caregivers.

Consideration for ways to develop EpxAutism in the future to meet further needs are extensive. Caregiver feedback indicating desire for more input is being examined. Currently, due to feedback from psychiatrists involved in the study, patients are being enrolled who will receive additional daily questions about quantity of meltdowns including dangerous behaviors (specifically self-injurious behavior, aggression, and disruption). Careful consideration will be taken not to drastically increase the number of daily messages and therefore subject users to increased message fatigue. Hand-written daily journals and optional free-text message responses for caregivers are potential solutions for caregivers who wish to provide more information while simultaneously avoiding overwhelming those who do not.

A natural extension to monitoring meltdowns in patients with ASD is empowering families with knowledge and guidance in order to reduce the quantity and duration of such episodes. EpxAutism is exploring using the Epharmix text messaging platform to periodically send caregivers information that teaches them to provide competent applied behavior analysis (ABA) techniques aimed at reinforcing appropriate behaviors and decreasing instances of inappropriate behaviors.

Children with ASD face additional risks that could be addressed via an automated text messaging platform. These children are at increased risk for fractures especially during childhood and adolescent development due to decreased bone density [58]. By monitoring mealtime behavior, dietary intake, physical activity, and screen time (time spent using electronic devices), risk for decreased bone density could be quantitatively measured remotely. In addition, children with ASD have increased rates of gastrointestinal symptoms, as well as changes in satiety and eating habits, compared to children without autism [59]. Thus, monitoring gastrointestinal symptoms, changes in weight, diet, and eating patterns could be a promising way to tailor text-based interventions for children with ASD.

Conclusion

Phone and text message interventions offer a promising, inexpensive platform to increase access to care for adolescent patients with depression and ASD and give providers a method to track symptoms and behaviors with unprecedented temporal resolution. The unique iteration cycle that we developed with Epharmix enables rapid conversion of feedback from patients and providers into optimized platforms for further testing. We envision EpxDepression and EpxAutism as stepping stones toward replacing traditional behavioral tracking, which is often limited by access and is biased by retrospective completion. While we discussed 2 interventions in this review, we developed a number of additional interventions within the scope of behavioral health and are currently running multiple pilot studies in parallel to confirm their clinical utility. Our goal is to leverage our rapid iteration cycles to develop a fully optimized mobile platform that can be tested in a Phase III RCT. While there are still many hurdles to overcome in adolescent psychiatry, the future standard of care may only be a text message away.

Acknowledgments

We would like to acknowledge the advice and aid of Avik Som, the Epharmix team, and their clinical partners in the development and implementation of this solution. We would also like to acknowledge the intellectual, technical, and logistical contributions of the Behavioral Health Network of Greater St. Louis, Dr Laura Bierut, and Dr Natasha Marrus.

Conflicts of Interest

This research was sponsored by Epharmix, Inc.

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Abbreviations

ABA: Applied Behavior Analysis
ASD: autism spectrum disorder
CATCH-IT: Competent Adulthood Transition with Cognitive-behavioral Humanistic and Interpersonal Training
CBT: cognitive behavioral therapy
cCBT: computerized cognitive behavioral therapy
CDRS-R: Child Depression Rating Scale Revised
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
MDD: major depressive disorder
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial

Edited by G Eysenbach; submitted 31.12.16; peer-reviewed by W Dalton, S Hatcher; comments to author 23.02.17; revised version received 05.04.17; accepted 24.04.17; published 16.06.17.

Please cite as:
Chen RY, Feltes JR, Tzeng WS, Lu ZY, Pan M, Zhao N, Talkin R, Javaherian K, Glowinski A, Ross W
Phone-Based Interventions in Adolescent Psychiatry: A Perspective and Proof of Concept Pilot Study With a Focus on Depression and Autism
JMIR Res Protoc 2017;6(6):e114
URL: http://www.researchprotocols.org/2017/6/e114/
doi:10.2196/resprot.7245
PMID:28623183

Publisher:
JMIR Publications
130 Queens Quay East.
Toronto, ON, M5A 3Y5
Phone: (+1) 416-583-2040
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